JULY 1955
VOL. XII NO 1

Circulation

FICIAL JOURNAL of the AMERICAN HEART ASSOCIATION

Annual Meeting of the American Heart Association
New Orleans, Louisiana, from October 22 — 26, 1955

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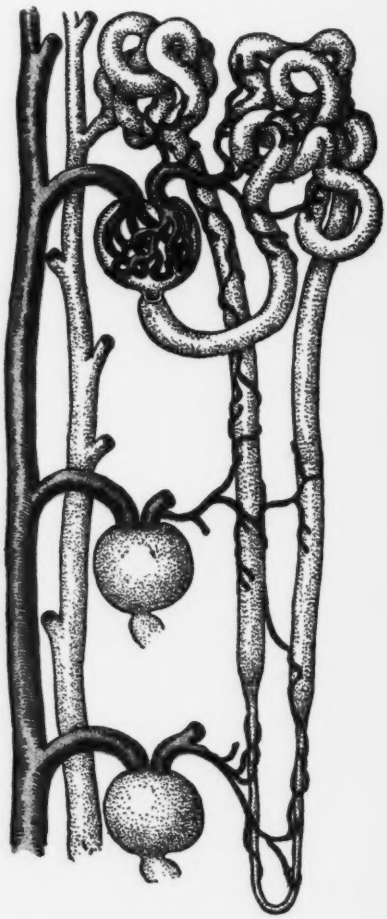

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JULY 1955
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OFFICIAL JOURNAL of the AMERICAN HEART ASSOCIATION

The Syndrome of Carcinoid and Acquired Valve Lesions of the Right Side of the Heart

By WILLIAM B. BEAN, M.D., DAVID OLCH, M.D. AND HARRY B. WEINBERG, M.D.

Recent papers by Biörck and Rosenbaum have revived interest in the rare disease characterized pathologically by carcinoid of the small intestine, metastases to the liver, acquired nonrheumatic disease of the tricuspid and pulmonic valve, and angiomas in the skin. Clinically the condition is characterized by dramatic episodes of flushing, mottling of the skin, diarrhea, dyspnea and ultimately by congestive failure. Probably 5-hydroxytryptamine (serotonin) liberated from the carcinoid tumors induces the vascular changes. The suggestion is set forth that an antagonist to this compound might reduce the symptoms and perhaps favorably affect the course of the disease. Two cases are reported.

DELINEATION of rare syndromes to advance our knowledge of medicine is erratic and may depend on whim or circumstance rather than concerted plan. Nonetheless by unraveling exotic disorders we may get welcome light on seemingly unrelated obscurities. Though rare diseases do not accumulate in large numbers, a lucid paper or a timely talk may catch the attention of many clinicians and what seemed rare is found to be merely uncommon.

Recently there has been a flurry of interest in the strange combination of carcinoid of the small intestine with metastases to the liver; acquired disease of pulmonary and tricuspid valves; and the clinical features of sudden irregular bursts of flushing of the skin with changing mottled cyanosis; diarrhea; "asthma" and finally edema and ascites.[1, 2] This witch's brew of unlikely signs and symptoms, intriguing to the most fastidious connoisseur of clinical esoterica, now has yielded clues which may help illuminate some aspect of valvular disorders of the heart in general.

One of us (W. B. B.) has studied vascular lesions in the skin for many years,[3, 4, 5, 6, 7] as well as certain aspects of induced flushing.[8] Before the recent reports of the carcinoid-cardiac syndrome we had studied a patient who fell into this category and had reviewed related medical reports, many of which have been reviewed.[1] One of us (H. B. W.) had observed another patient. It is our purpose to report these two cases, call attention to reports of other probable ones, and present a suggestion about treatment.

CASE REPORTS

Patient 1. L. R. O. was a 42-year-old white housewife. She was admitted to the Medical Service of the University Hospitals on Aug. 29, 1951 with the main complaint of diarrhea and unusual skin lesions. She had been in good health until 18 months before admission when, rather abruptly, she developed diarrhea with about six loose, watery stools daily. There had been several tarry stools but no fresh blood or mucus. When this trouble was beginning she had generalized abdominal cramps. They lasted for about two weeks and then subsided. The diarrhea persisted. During the year before admission, she noticed recurrent erythema of the

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Aided by the Department of Medicine Trust Fund.

skin over the trunk, abdomen and face. The cheeks and bridge of the nose became blotched. There was a bizarre, rapid and unpredictable change in the distribution and indeed the character of the lesions. They were always aggravated by heat or pressure. The skin of the lower abdomen, back and lower extremities was continuously cyanotic. There was progressive weakness. She was tired, had no appetite and at times had nausea. She had no fever or chills but had lost 40 pounds. During the month prior to admission she had persistent nonpitting edema of the ankles. It was reduced, but not eliminated, by mercurial diuretics. She had mild exertional dyspnea during that period.

About six months before admission small petechiae appeared on her arms. They persisted at the time of her admission. There was no history of rheumatic fever or congenital heart disease. She had had grand mal epilepsy for 10 years, well controlled with Dilantin for the past four years. A subtotal hysterectomy had been done 11 years prior to admission for reasons unknown.

Physical examination. The patient was a chronically ill white woman who had lost much weight. She looked her age. The skin underwent rapid and extreme changes during the examination, the like of which none of us had seen before. A recurring alternating pink and erythematous blotchy bluish discoloration occurred over the chest, abdomen and back (fig. 1). The changes resembled giant urticaria with geographical outlines but the edges were not raised. A complete transformation in the lesions might occur, a whole new pattern appearing within three to five minutes resembling in clinical miniature the fickle phantasmagory of the Aurora Borealis. The bluish mottling of the trunk and lower extremities remained constant. There were scattered petechiae over the arms and legs. Some of the larger lesions had thick indurated edematous surfaces projecting above the level of the skin.

There was generalized lymphadenopathy affecting mainly cervical, axillary and inguinal nodes which were firm and fixed to the surrounding tissue. Petechiae were noted on the buccal mucosa. The neck veins were distended. They had prominent pulsations. The chest was symmetrical. The lungs were normal. The breasts were atrophic without scars or lumps.

The heart had an overactive right ventricle; the sounds were of good quality; the rhythm regular. The left cardiac border was in the midclavicular line. The second pulmonic was greater than the second aortic sound, and the first apical sound was accentuated. A harsh, blowing systolic murmur was heard to the right of the sternum in the second intercostal space. It was heard well in the pulmonic area and was transmitted to the neck. At the apex there was a systolic murmur and a low pitched rumbling diastolic murmur. Arterial blood pressure was 100/60. The peripheral pulses were palpable. Oscillometric readings were normal.

The abdomen was flat but the liver was palpable in the right upper quadrant extending 5 cm. below the rib margin. The spleen and kidneys were not felt. Vaginal and rectal examinations were not unusual. The test for occult blood in the stool was negative. In addition to the mottled discoloration of the legs, there was 4 plus non-pitting edema of the ankles and legs. The neurological examination was normal.

Laboratory tests yielded these results: the urine had a specific gravity of 1.013 and was negative.

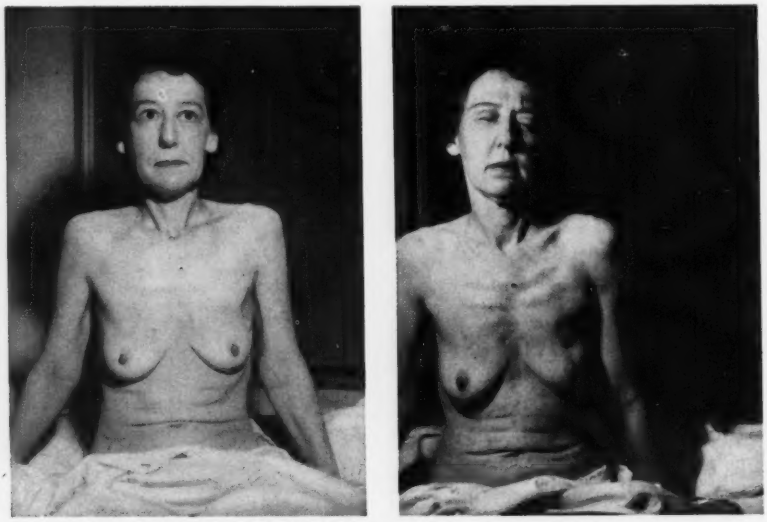

FIG. 1. Color photographs of the flushing taken one minute apart.

The hemoglobin was 12 Gm., red blood cell count 4.3 million, and the white cell count was 7,350 with 54 per cent neutrophils, 38 per cent lymphocytes, 6 per cent monocytes and 2 per cent eosinophils. Serologic test for syphilis was negative. The sedimentation rate was 7 mm. in 1 hour (Westengren). Bleeding time was 1 minute. Coagulation time was 4 minutes. Clot retraction was complete. Prothrombin time was 15.5 seconds with a control of 15.5. The platelet count was 130,000. The serum proteins were 6.16 Gm. per 100 cc. with 3.86 Gm. of albumin and 2.3 Gm. of globulin. The cephalin flocculation test was negative at 24 and 48 hours. Bromsulfalein retention was 2 per cent at the end of 45 minutes. The Rumple-Leeds test was negative. Spinal fluid dynamics and chemical tests were normal.

Fluoroscopic examination of the heart showed definite right ventricular in- and outflow path enlargement without demonstrable left auricular enlargement. Films and fluoroscopic study of the colon with barium showed decrease in haustral markings and slight serration in the sigmoid portion. Upper gastrointestinal x-ray studies, skull films and pneumoencephalogram were negative. The electrocardiogram was normal. One of the petechiae removed from the right deltoid region revealed patchy perivascular edema and lymphocytic infiltration into the blood vessels of the derma (fig. 1) The epidermis and dermal adnexae were normal. The muscle itself was normal. Sternal bone marrow was hypocellular. There were no lupus erythematosus cells.

Routine agglutinations for brucellosis, typhoid fever and paratyphoid were negative. Complement fixation test for amebiasis was positive. No ova or parasites could be found in the stool and the sigmoidoscopic examination was normal. Nonetheless she was given a course of antiamebic therapy with Diodoquine and Chloroquine. No improvement occurred.

She left the hospital unimproved, undiagnosed and untreated. Her continually declining health caused her to enter the hospital in her home town where skin biopsy was repeated with the same findings. A lymph node from the right inguinal region showed calcification. Tests for hemochromatosis were negative. Serum calcium was 14 mg. per 100 ml. with normal phosphorus and phosphatase. X-ray films revealed normal long bones but calcification was seen in the soft tissues around the upper humerus and along both femurs. Her liver gradually enlarged. She continued to deteriorate, grew progressively weaker and died March 30, 1952.

Necropsy. Postmortem examination revealed a thin woman with little subcutaneous fat. The skin was thickened and adherent over the chest, abdomen and lower extremities. No tumors were found in the breast.

The liver was enlarged, dark brown in color and contained many metastases varying from 0.5 mm. to 3.5 cm. in diameter. The masses on the surface

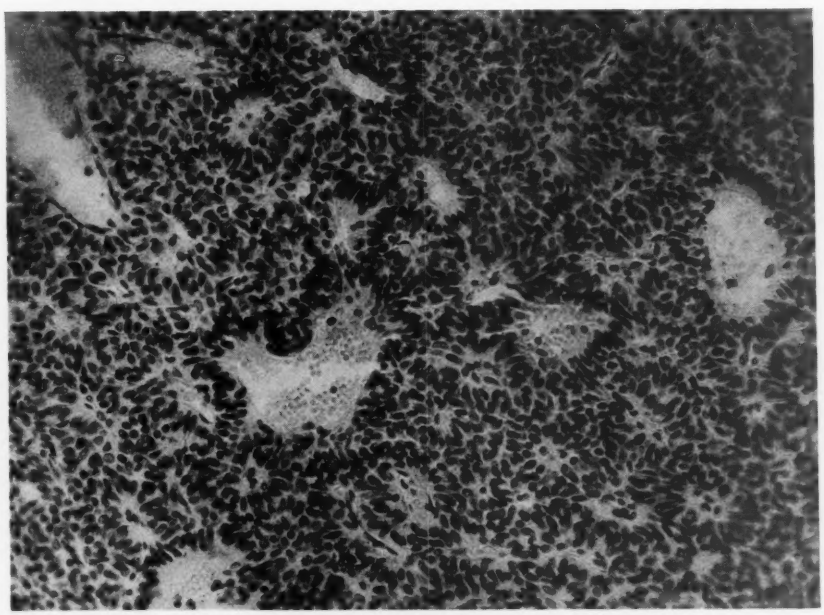

FIG. 2. Microscopic section of the carcinoid tumor with nests and acinar formation in a stroma of connective tissue.

of the liver were umbilicated and some of the larger tumor masses had central necrosis with hemorrhage. The stomach was much dilated with a large amount of coffee ground material. The small bowel was red to black in color. At the junction of the jejunum and ileum a small mass in the wall of the bowel produced a right angle kink with obstruction. At this point there was gangrene with peritonitis involving the small bowel and cecum.

The heart was of normal size. On section the tricuspid and mitral valves were much thickened. The tendinous cords were thickened and sclerotic. The pulmonic and aortic valves had great thickening and contraction of the valve flaps. There was no obvious arteriosclerosis.

The microscopic study revealed a malignant tumor of the ileum characterized by nests or columns of cells surrounded by stroma of connective tissue. The cells were fairly regular in outline and had a distinct nucleus without nucleolus. Some cells formed a definite acinar pattern (fig. 2). The pathologic diagnosis was carcinoid of the ileum metastasizing to the liver.

The skin showed much sclerosis together with atrophy (fig. 3). Some of the abdominal skin showed areas of generalized telangiectasia without scleroderma.

In spite of the marked sclerosis of the cardiac valves there was no lesion of rheumatic heart disease.

Patient 2. M. E., a 43-year-old business man, first came to consult one of us (H. B. W.) on April 7, 1950, complaining of flushing attacks and something the matter with his heart. Some years previously he had been told that he had a heart murmur but he had no cardiac symptoms until three weeks before the first visit. Flushing spells began two months after an appendectomy, nine months before he was first seen. He had consulted several doctors and visited different clinics where he was told that he had congenital heart disease or rheumatic heart disease. Three weeks before his visit he noticed that he was gaining weight and was having exertional dyspnea but no orthopnea or paroxysmal nocturnal dyspnea. A week later ankle edema first appeared. It diminished with the employment of a low salt diet and digitalis. Most of the flushing attacks were very mild and transient, just flushing and subjective warmth of the face; but four attacks were very severe and had lasted a long time. In those attacks he also had flushing of the hands and swelling of the eyelids and lips. After the flush and the heat left, pallor might occur. The swelling receded slowly. At times there was palpitation with the flushing but usually there was not. There was no pain, lacrimation, rhinorrhea, shortness of breath, hunger, headache or sweating. With the severe attacks there was some apprehension and dizziness. There was no premonitory warning. He knew of nothing he did to bring on the attacks or to stop them.

Initial physical examination revealed a well developed, fairly well nourished white man who was not acutely ill or in discomfort. He weighed

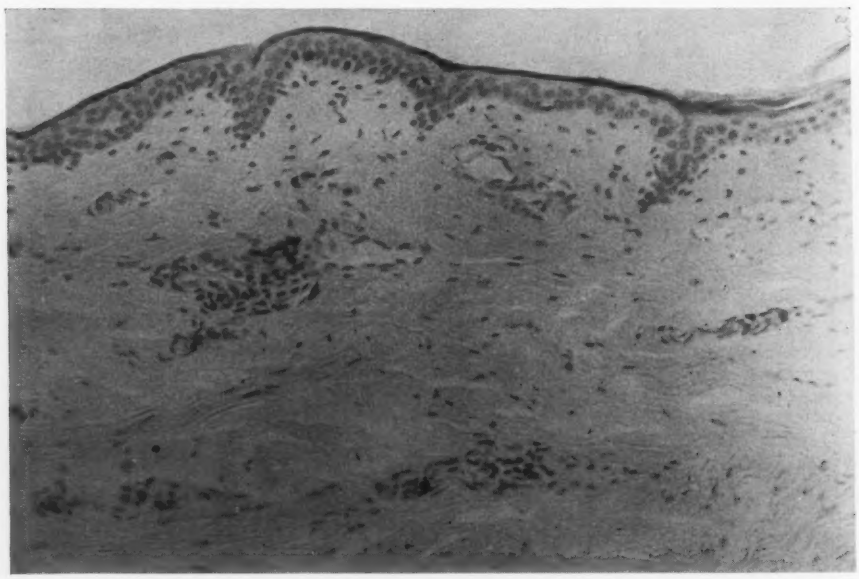

FIG. 3. Lesion of skin with dilated thin walled vessels and sclerotic changes. The papillae are flattened.

167 pounds. Very prominent venous pulsation was seen at the base of the neck bilaterally. There were three visable pulsations and two thrusts were palpable, one systolic and one presystolic. The heart was not enlarged. The first tone was replaced by rough systolic murmur. It was maximal in the fourth left intercostal space and well transmitted to the right sternal border and upward into the neck. It was not so loud over the pulmonic area or at the apex but was heard in the axilla. Two diastolic murmurs were heard over the lower right half of the precordium, giving a quadruple rhythm. No diastolic murmur was heard at the apex. The rhythm was regular. The rate was 82, the blood pressure 120/80. The liver was felt 4 cm. below the edge of the ribs. It was soft but not tender. Fluoroscopic examination showed a normal left border. The right border was a little prominent. In the right anterior oblique position, there was no conus fullness. The retrocardiac space was clear. There was no displacement of the barium filled esophagus. An electrocardiogram showed the typical pattern of incomplete right bundle branch block.

The urine was negative. The Wassermann and Kline reactions were negative. Complete blood studies were normal except for the sedimentation rate which was 15 mm. in 1 hour (Cutler). Vital capacity was 3.5 liters.

On subsequent visits the venous pulsations in the neck were clearly identified as presystolic in time. The systolic murmur was audible over a wide area. The diastolic murmur was still heard over the right half of the precordium. He had several more flushing attacks. During a vacation he did not remain on a strict diet and developed some edema. At a subsequent examination repeated transitory flushing was observed. It was brief and resembled a severe flush of embarrassment, though more extensive, affecting the entire face and the bald area of the scalp. Two months after the initial examination he had lost 18 pounds, looked and felt extremely ill and was undergoing continuous flushing during the entire examination. The liver was larger and was moderately tender. The urine now contained albumin and casts. He was again seen by several doctors and in other clinics, finally admitted to another hospital where a preoperative diagnosis of pericarditis was made. At operation the heart was found to be normal. His death occurred 14 months after he was first seen and approximately two years after his first symptom.

The *autopsy findings* included: malignant carcinoid of the ileum with metastases to the liver, lymph nodes and posterior parietal peritoneum and valvulitis involving all the cardiac valves but most marked in the pulmonic and tricuspid valves.

Discussion

Since the syndrome under discussion has been reviewed recently[1] we will not cite the collected cases. Parkes Weber[9, 10] has dealt with the syndrome, though he did not give details of a case he mentioned. Most recent authors have overlooked the observations of Steiner and Voerner[11] recorded in 1909 under the title of Miliary Angiomatosis. They described a 27-year-old man with generalized miliary telangiectases over his whole body. He had severe flushing of the face, body and trunk. A biopsy of the skin showed telangiectasia, formation of new vessels and thrombosis of the larger dilated vessels. The man was under observation for five months. There were no later reports.

We can see no real resemblance of the clinical features of this syndrome to the crisis of pheochromocytoma, the vasomotor storm of thyrotoxicosis, the mottled flush of the diencephalic hypertensive[12] or diencephalic epilepsy, the unilateral flush-sweat of Madame Frey's syndrome or the unilateral burst of flushing seen in very young infants.

The production of serotonin[13] by carcinoid tumors has been demonstrated recently by Lembeck.[14] The possible mechanism by which a potent vasodilating substance, manufactured in the liver, thrown suddenly in potent concentration into the right side of the heart, might damage directly the mural endocardium and the tricuspid and pulmonary valves, is speculative. The clinical features of waves of vasodilatation suggest irregular intermittency and varying concentrations of the agent which must traverse at least the pulmonary capillaries, and perhaps those of the liver.

The brilliant studies of Woolley[15, 16] on biological and molecular antagonists against serotonin suggest that an antagonist might, by neutralizing or blocking its effect, relieve symptoms. It is less likely, but possible, that as an antagonist against the product of a tumor it might inhibit its growth.

Patients with the carcinoid-cardiac syndrome, though not common, present us with a chance to explore new physiologic terrain with equipment already at hand. If for no other reason this justifies our report of these two unusual patients.

Conclusion

We have reported two patients with typical clinical features of 1) patterned irregular

flushing which comes and goes abruptly, 2) mottled cyanosis, 3) diarrhea, 4) asthma, 5) signs of valvular lesions of the right side of the heart and 6) edema and congestive failure. The pathologic findings are 7) carcinoid of the small intestine with metastases to the liver, 8) unusual lesions of the tricuspid and pulmonic valves and 9) telangiectasia with a proliferative and thrombotic disorganization of blood vessels of the skin.

We subscribe to the suggestion of others that this unlikely combination of symptoms and lesions is best explained on a humoral basis; that the carcinoid manufactures serotonin, and releases it into the inferior vena cava erratically; that this in some way produces a morphologic turmoil in valves and endocardium of the right side of the heart, and the torment of brisk and sometimes ephemeral flushing.

We suggest that a molecular antagonist to serotonin should be tested as a possible agent of palliation or cure.

Conclusion in Interlingua

Nos presenta le casos de duo patientes con le sequente "improbabile" combination de symptomas e lesiones:

Clinicamente le casos se distingueva per 1) rubor a contorno irregular e apparition e disparition abrupte, 2) cyanosis marmorate, 3) diarrhea, 4) asthma, 5) signos de lesiones valvular del latere dextere del corde, e 6) edema e dysfunctionamento congestive. Le constatationes pathologic esseva 7) tumor carcinoide del intestino tenue con metastases del hepate, 8) lesiones inusual del valvulas tricuspide e pulmonic, e 9) telangiectasia con disorganisation proliferative e thrombotic del vasos sanguinee del pelle.

Nos nos trova de accordo con le opinion de altere autores que un tal syndrome se explica le melio super un base humoral, i.e. que in illo le tumor carcinoide produce serotonina e disbucca lo erraticamente a in le vena cave inferior e que assi il adveni in alicun maniera un disordine morphologic del valvulas e del endocardio al latere dextere del corde e postea le tormento del vive e a vices ephemere rubor.

Nos opina que le cerca de un possibile agente palliative o curative deberea concentrar se super le essayage de antagonistas molecular de serotonina.

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Circulatory Effects of Mitral Commissurotomy with Particular Reference to Selection of Patients for Surgery

By M. Irené Ferrer, M.D., Réjane M. Harvey, M.D., Robert H. Wylie, M.D., Aaron Himmelstein, M.D., Adrian Lambert, M.D., Marvin Kuschner, M.D., André Cournand, M.D. and Dickinson W. Richards, M.D.

Of 60 patients with mitral stenosis referred as proper candidates for commissurotomy, less than half (27) proved suitable after further study. One half of these (13) had a good postoperative result as judged not only clinically but by objective physiologic measurements. The latter represent the best criteria for the effects of surgery since subjective impressions may be unreliable. Eight subjects originally advised to undergo surgery would now be rejected inasmuch as myocardial insufficiency and not mitral block was their predominant difficulty. Clinical criteria appear as yet inadequate for the selection of the proper candidate for mitral commissurotomy, as there is no good clinical means of establishing in every instance the presence of pulmonary hypertension which remains the best evidence of a significant degree of mitral block.

SINCE Bailey[1, 2] and Harken[3] have demonstrated the feasibility of the surgical approach to the problem of mitral stenosis, patients with this lesion are being re-evaluated in numerous clinics with the possibility of commissurotomy in mind. It is well to remember that surgical treatment is directed at the relief of the mechanical difficulties imposed by mitral valve obstruction. It has been postulated and recently re-emphasized[4-6] that chronic pulmonary hypertension is one of the chief resultants of significant mitral block. This postulate has been confirmed by physiologic studies which also showed decrements in pulmonary artery pressures after successful mitral surgery.[2, 7-9] Thus, it has become established that operative intervention can alleviate at least some of the consequences of mitral block. However, it has also been found that mortality is high in the markedly incapacitated rheumatic subject and therefore it has appeared that one should relieve mitral block before its effects reach an advanced stage. As a consequence of this type of reasoning, less and less attention is being directed at establishing that the symptoms and physiologic derangements of the patient with mitral stenosis are due predominantly to obstructive mitral block. Indeed, at the present time, if a patient has mitral stenosis and symptoms referable to the cardiorespiratory systems it has become almost axiomatic to ascribe these symptoms to a small mitral orifice and offer the patient surgery.[10, 11] Hence the criteria for the selection of patients for commissurotomy have become entirely clinical, based on signs and symptoms which are not specific to mechanical mitral block, and little or no attempt is being made to identify the presence of pulmonary hypertension except by inference.[5, 6, 8]

The present report has been prepared on the basis of material accumulated over the past five years, in an attempt to focus more precisely upon the nature of the circulatory dysfunction produced by mitral block, to evaluate the effects produced by commissurotomy, and to define more specifically, if possible, the suitable candidate for this

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The work described in this paper was supported by a grant from the Life Insurance Medical Research Fund, and by a research grant (PHS Grant H-833 (C)) from the National Heart Institute of the National Institutes of Health, United States Public Health Service.

surgical procedure. Hemodynamic measurements coupled with clinical observations were utilised to define the patient's circulatory function prior to surgery as well as to establish the postoperative status. Early in our experience it became apparent that these hemodynamic data were essential to the evaluation of the surgical results of a procedure following which patients, desperately ill and anxious for relief, reported all grades of improvement. For adequate final appraisal objective measurements had to be available against which to titrate these subjective expressions of benefit.

This paper presents the experience of the authors with a group of patients referred to us as possible candidates for commissurotomy and includes our method of evaluation of the patient with mitral stenosis, as well as the results of commissurotomy when this operation has been performed.

Method of Study

In the past five years 60 patients with mitral stenosis have been considered as possible candidates for mitral commissurotomy. The majority of these subjects were referred to us by their local physicians as suitable candidates. Prior to any decision regarding surgery, all these patients were closely observed in order to rule out not only such complications as active rheumatic carditis, subacute bacterial endocarditis and intractable heart failure, but also to establish the best possible status obtainable by medical means prior to evaluation by cardiac catheterization. This period of observation in the hospital lasted two to three weeks in most instances, but was extended to four or five months in several patients.

The method of physiologic appraisal, using the cardiac catheterization technic, has been detailed in a previous report,[12] which also contains the criteria for interpretation of results. In this regard, it is important to stress the difficulties and potential errors which arise when one endeavors to compare catheterization studies made at two different times in an effort to determine the effect of a single alteration of the circulatory dynamics such as mitral valve commissurotomy. For example, if the patient s not in the same metabolic state each time, variations in the cardiac output may be expected; if there has been a change in cardiac rhythm cardiac output may also vary and of course, variations in output may in turn alter right heart pressures as well; if the heart rate fluctuates markedly, right heart pressures may also change; if heart failure was present before surgery and is absent thereafter, this too will cause dynamic alterations in both flow and pressures. Any one of these changes occurring postoperatively could mask the true effects of surgery. Hence every effort has been made to recognize these factors in our interpretation of results, and to avoid the potential errors whenever possible.

The operative procedure in those patients who came to surgery was carried out using in general the technic of Glover and Bailey.[13] The majority of the cases were operated upon by members of the surgical team (R. H. W., A. H., A. L.). Through the courtesy of Doctors Lawrence Miscall and Jere Lord it was possible to study five additional patients.

Results

The 60 patients referred to this clinic for surgery were considered to have met the clinical criteria by the referring physicians and the majority were willing and even anxious to undergo operation. Furthermore, it should be specifically noted that no one was accepted by the authors for evaluation unless enlargement of the left ventricle and intractable heart failure had been excluded and these types of rheumatic patients are not included in this presentation.

Patients rejected after clinical study alone. Fifteen patients were rejected as possible candidates for operation after further careful clinical observation only. Of these, 10 proved to have active rheumatic carditis and five subacute bacterial endocarditis as judged by the usual clinical criteria. In all 15, these conditions were previously unsuspected or unproven. One of the subjects with subacute bacterial endocarditis was cured and became a candidate after one year's time (case 700, tables 2, 3).

Patients rejected after physiologic study. Fifteen of the remaining 45 patients were rejected after physiologic study and the reasons for rejection will be considered below. Their diagnoses and data appear in table 1. Four of the 15 patients (group A, table 1) were not offered surgery because pulmonary artery pressures and cardiac outputs were normal at rest and pulmonary artery pressures were essentially unchanged during exercise. In two patients (cases 767 and 650) blood flow rose normally during exercise although in the third

TABLE 1.—*Clinical and Physiologic Data in 15 Patients Rejected for Surgery who had Rheumatic Mitral Stenosis without Mitral Block*

Case, Sex, Age	Diagnosis	Symptoms	Cardiac Index (L/min./M² BSA.)	Pulmonary Artery s/d, m (mm. Hg)
Normal at rest			3.12 ± 0.4	<30/10, 15
		(A) *No Definite Physiologic Abnormality*		
*767. LD. F. 34 yrs.	MS. SA. Inc. AV block	Fatigue	(R) 2.66 (E) 3.77	13/7, 11 13/8, 10
*650. WG.† M. 27 yrs.	EH. MS. MI. NSR.	Hemoptysis	(R) 3.05 (E) 4.36	15/5, 8 18/8, 13
*694. MF. F. 30 yrs.	EH. MS. MI. AI. NSR.	Dyspnea, palpitations	(R) 2.93 (E) 3.28	21/10, 14 25/12, 18
*741. MK. F. 36 yrs.	EH. MS. MI. NSR. APC'S.	Fatigue	(R) —	24/9, 15
		(B) *Myocardial Insufficiency*		
695. SB. F. 44 yrs.	EH. MS. NSR.	Bouts of CHF.	(R) 1.98 (E) 2.27	27/16, 20 30/15, 21
675. JH. M. 41 yrs.	EH. MS. AF.	Previous bout of CHF.	(R) 3.46 (E) 3.84	28/12, 21 39/18, 27
591. NG. M. 32 yrs.	EH. MS. AI. NSR.	Fatigue, dyspnea	(R) 2.90 (E) 3.97	23/9, 16 51/27, 39
761. MD. F. 42 yrs.	EH. MS. AF.	Palpitations	(R) 2.08 (E) 2.52	30/17, 22 50/33, 41
552. JS. M. 52 yrs.	EH. MS. AF.	Bouts of CHF.	(R) 2.33 (E) 3.20	29/13, 19 49/25, 33
*782. LL. F. 32 yrs.	EH. MS. MI. NST.	Fatigue, dyspnea, one bout of AF.	(R) 3.23 (E) 3.86	18/11, 14 32/19, 25
*641. DK. F. 44 yrs.	EH. MS. MI. (T.I.) AF. VPC'S.	Dyspnea, palpitations	(R) 3.19	29/13, 19
		(C) *Myocardial Insufficiency With Frank Left Ventricular Failure*		
*555. EB.† F. 29 yrs.	EH. MS. (T.I.) AF. Healed SBE.	Bouts of CHF, dyspnea	(R) 2.15	40/16, 25
*612. CE.† M. 20 yrs.	EH. MS. MI. (G-S) NST.	Dyspnea, CHF.	(R) 2.39	79/42, 57
		(D) *Mild Pulmonary Hypertension Of Uncertain Etiology*		
*715. FT. M. 29 yrs.	MS. SA.	Hemoptysis	(R) —	32/18, 24
*620. RF. M. 43 yrs.	EH. MS. SA.	Dyspnea	(R) 3.72	35/19, 27

* Complete hemodynamic data previously published.[12]
† Complete hemodynamic data previously published.[14]
For additional abbreviations see end of table 3.

TABLE 2. *Summary of Clinical, Hemodynamic and Pathologic Findings in 27 Patients Selected for Mitral Commissurotomy*

Case Sex, Age	Diag.	Pre-op. Physiol. Status	Post-op. Clin. Result	Post-op. Physiol. Result	Character of Mitral Valve	Auric. Append. Biopsy
#567. JC. M. 35 yrs.	EH. MS. (T.I.) AF.	† Severe pul. hyp. and low CO at rest.	Excellent; now 4¼ yrs. post-op.	Marked fall in pul. hyp. and rise in CO at 11 months.	Conical. Leaflets supple with fibrous ring at orifice.	Organized thrombus in appendage.
#595. AB. M. 28 yrs.	EH. MS. AI. NSR.	† Mod. pul. hyp. and low CO at rest.	Excellent; now 4 yrs. post-op.	Fall of PA pressures to normal but no change in CO at 1 year.	Conical. Leaflets supple. No thickening.	Aschoff bodies.
#618. HI. F. 41 yrs.	EH. MS. (T.I.) AF.	† Severe pul. hyp. and low CO at rest.	Excellent; now 3⅓ yrs. post-op.	Fall in pul. hyp. and no change in CO at 1 month.	Conical. Leaflets supple but diffusely thickened.	Organized thrombus in appendage.
#703. MA. F. 53 yrs.	EH. MS. (G-S) NSR.	† Severe pul. hyp.	Excellent; now 2 yrs. post-op.	Fall in pul. hyp. at 6 months.	Conical. Heavily fibrotic at orifice but leaflets supple elsewhere.	No Aschoff bodies.
#707. CC. M. 36 yrs.	EH. MS. (G-S) SA.	† Severe pul. hyp. and low CO at rest.	Excellent; now 20 mos. post-op.	Marked fall in pul. hyp. but no change in CO at 2 months.	Conical. Granular calcif. at slit-like orifice but leaflets supple and thin elsewhere.	Aschoff bodies.
#714. RD. M. 29 yrs.	EH. MS. SA.	† Severe pul. hyp. and low CO at rest.	Excellent; now 19 mos. post-op.	Fall in pul. hyp. but no change in CO at 6 weeks.	Flattened cone. Calc., eliptical orifice with ebernated edges. Leaflets thick. Sl. restricted motion of ant. leaflet.	No Aschoff bodies.
#713. EW. F. 28 yrs.	EH. MS. (G-S) NSR.	† Severe pul. hyp. and low CO at rest.	Excellent; now 16 mos. post-op.	Marked fall in pul. hyp. and rise in CO at 1 year.	Conical. Leaflets supple, thin and mobile.	Aschoff bodies.
#659. EB. F. 46 yrs.	EH. MS. (G-S) NSR.	§ Severe pul. hyp. and low CO at rest.	Excellent; now 1½ yrs. post-op.	No study.	Discoid. Heavy granular calcif. throughout. Poor motion of leaflets. Short thickened chordae tendinae.	Suggestive of auriculitis
#633. GS. M. 28 yrs.	EH. MS. I.AV.B. NST.	§ Severe pul. hyp. and normal CO at rest.	Good; now 3¼ yrs. post-op.	Marked fall in pul. hyp. and CO at 9 months.	Conical. Calc. at orifice but leaflets supple elsewhere.	Endocardial thickening.
#663. LS. F. 37 yrs.	EH. MS. NSR.	† Mod. pul. hyp. and normal CO at rest.	Good; now 2¾ yrs. post-op.	Fall in pul. hyp. and no change in CO at 1 year.	Funnel-shaped. Leaflets diffusely thickened.	Aschoff bodies.
#744. LD. F. 29 yrs.	EH. MS. NSR.	§ Severe pul. hyp.	Good; now 12 mos. post-op.	No study.	Conical. Leaflets supple with fibrotic ring at orifice.	Aschoff bodies.
#722. IK. F. 32 yrs.	EH. MS. NSR.	§ Mod. pul. hyp.	Good; now 16 mos. post-op.	Slight fall in resting pul. hyp. at 14 months.	Conical. Leaflets supple with slight calcif. and thickening at orifice.	Aschoff bodies.

*792. MH. F. 41 yrs.	EH. MS. AF.	§ Severe pul. hyp. and low CO at rest.	Good; now 6 mos. post-op.	Marked fall in pul. hyp. and rise in CO at 6 months.	Conical. Leaflets pliable.	Aschoff bodies.
*664. JZ. M. 26 yrs.	EH. MS. NSR.	§ Severe pul. hyp. and normal CO at rest.	No change at 7 mos. Is now 2 yrs. post second commissurotomy but still unimproved.	No change in pul. hyp. but fall in CO at 7 months after first operation.	Conical. Calcif. Small regurg. jet post-op.	No Aschoff bodies.
*699. FB. M. 27 yrs.	EH. MS. AI. AF.	‡ Mild pul. hyp. and normal CO at rest.	No change; now 2 yrs. post-op.	No change in pul. hyp. but fall in CO at 6 months.	Conical. Granular calcif. at orifice but leaflets supple elsewhere.	Organized thrombus in appendage.
*635. GB. M. 39 yrs.	EH. MS. AF.	‡ Mild pul. hyp. and low CO at rest.	No change; now 3¼ yrs. post-op.	No change in pul. hyp. or CO at 1 month.	Conical. Leaflets supple, diffusely thickened.	Organized thrombus in appendage.
*627. EB. F. 30 yrs.	EH. MS. (G-S) NSR.	§ Severe pul. hyp. and low CO at rest.	Died suddenly 3 yrs. post-op.	Slight fall in pul. hyp. and marked fall in CO at 15 months.	Discoid. Fibrous ring at orifice and leaflets diffusely thickened.	Endocardial thickening. No necropsy.
*606. PT. M. 49 yrs.	EH. MS. MI.* SA.	§ Mod. pul. hyp. and low CO at rest.	Died 3¼ yrs. post-op.	No change in pul. hyp. but fall in CO at 1 year.	Rigid diaphragm. Calc. Regurg. jet, reduced post-op.	Aschoff bodies. (No evidence of activity at necropsy.)
*538. GT. M. 25 yrs.	EH. MS. MI. SA.	§ Mod. pul. hyp. and low CO at rest.	Died 10 mos. post-op.	No study.	Conical. Calcified. Regurg. jet pre- and post-op.	Aschoff bodies. No necropsy.
*649. JW. M. 42 yrs.	EH. MS. MI. (T.I.) AF.	§ Severe pul. hyp. and low CO at rest.	Died suddenly 2½ yrs. post-op. (No commissurotomy done).	Fall in pul. hyp. and rise in CO at 1 month.	Obviously insufficient with regurg. jet. Calcif. at edges. No valve closure in systole.	Inadequate specimen. No necropsy.
*723. FH. M. 37 yrs.	EH. MS. MI.* (G-S) NST.	§ Severe pul. hyp. and very low CO at rest.	Died 10 days post-op. (No commissurotomy done).	No study.	Discoid. Heavily calc. Very poor motion of valve. Slit-like eliptical orifice with large regurg. jet. No closure of valve in systole.	No Aschoff bodies. (No evidence of activity at necropsy.)
*751. JD. M. 32 yrs.	EH. MS. MI.* AF.	§ Mod. pul. hyp. and low CO at rest.	Died in CHF 6 wks. post-op. (No commissurotomy done).	No study.	Discoid. Scarred, shriveled post. med. leaflet. Ant.-lat. leaflet calcif. and hard. Gross regurg.	Aschoff bodies. (Aschoff bodies in left ventricular myocardium at necropsy.)
*662. NW. F. 26 yrs.	EH. MS. TS.* NSR.	§ Mod. pul. hyp. and low CO at rest.	Operative death.	No study.	Funnel-shaped. Heavily fibrotic at orifice, leaflets moderately supple elsewhere. Regurg. jet felt pre-op.	Aschoff bodies. (Active auriculitis and myocarditis at necropsy.)

TABLE 2.—*Cont.*

Case Sex, Age	Diag.	Pre-op. Physiol. Status	Post-op. Clin. Result	Post-op. Physiol. Result	Character of Mitral Valve	Auric. Append. Biopsy
#607. CC. F. 35 yrs.	EH. MS.* (G-S) AF.	§ Severe pul. hyp. and low CO at rest.	Operative death.	No study.	Funnel-shaped. Leaflets leathery.	Organized thrombus in appendage. (No activity at necropsy.)
#622. JB. M. 36 yrs.	EH. MS.* (T.I.) (G-S) AF.	§ Severe pul. hyp. and low CO at rest.	Operative death.	No study.	Funnel-shaped. Leaflets markedly thickened.	Organized thrombus in appendage. (Active tricuspid endocarditis at necropsy.)
#609. JB. M. 34 yrs.	EH. MS.* NSR.	§ Severe pul. hyp. and low CO at rest.	Operative death.	No study.	Conical. Heavily calcified.	No Aschoff bodies. (No evidence of activity at necropsy.)
#700. AC. M. 42 yrs.	EH. MS.* (G-S) RBBB. NSR. Healed SBE.	§ Severe pul. hyp. and low CO at rest.	Operative death.	No study.	Discoid. Extensive calcif. especially in ant. leaflet.	Aschoff bodies. (Active auriculitis and myocarditis at necropsy but no evidence of SBE.)

* Confirmed by necropsy.
† Complete hemodynamic data can be found in table 1 of the accompanying report.[12]
‡ Complete hemodynamic data can be found in table 2 of the accompanying report.[12]
§ Complete hemodynamic data can be found in table 3 of this paper.

PA = pulmonary artery.
Mod. = moderate.
Pul. hyp. = pulmonary hypertension.
CO = cardiac output.
Calcif. = calcification
Calc. = calcified
For additional abbreviations see end of table 3.

(case 694) the cardiac output response was probably somewhat less than normal.

The cardiac nature of their disability, as expressed by these four patients, was never completely convincing clinically. From the hemodynamic data one can conclude that two patients (cases 767 and 650) had normal circulatory function as measured. In the remaining two, the presence of normal pulmonary artery pressures probably eliminates significant mitral block.[12] Once their circulatory status had been clarified, it became easier to define the true nature of their complaints. Observations over a one to three year period have shown that psychiatric illness (case 767), respiratory infections (case 650), neurosis (case 694) and alcoholism (case 741) were the bases, respectively, of their symptoms.

In contrast to the previous group, the seven patients in group B, table 1, had unequivocal and objective clinical evidences of cardiac disability. As indicated in this table, five of the seven have been discussed extensively in a previous report[12] and their disability ascribed primarily to myocardial insufficiency rather than to mitral block since their dysfunction was associated with little or no resting pulmonary hypertension. The last two subjects (cases 782 and 641) were in no way different from the other five in this group. It is of interest that one of these (case 782) had had the same pulmonary artery pressures at rest 19 months before, indicating no recent change in hemodynamic status.

Although both patients in group C, table 1, had pulmonary hypertension at rest, these individuals were not offered surgical treatment because acute Digoxin studies, details of which have been previously published,[14] uncovered a significant degree of left ventricular myocardial failure contributing to the elevated pulmonary artery pressures. It is evident that patients with mitral stenosis in whom left ventricular failure has been shown to account, at least in part, for the pulmonary hypertension cannot be considered for mitral surgery as there is as yet no positive way of excluding intractable left ventricular failure as being the sole or predominant cause of their disability.

In the last two subjects of the 15 rejected for surgery (group D, table 1) unequivocal objective evidences of disability were lacking and it was difficult to learn if there existed any diminished cardiac reserve in these two men in whom alcoholism was a major problem. Physiologic studies uncovered a mild degree of resting pulmonary hypertension in both, which could be the resultant of either myocardial insufficiency and some degree of left ventricular failure or mitral block. Since one could not be certain of their true status, and since their symptoms were not disabling, it was decided not to offer them surgery. The decision to withhold surgery in these two patients with minimal hemodynamic abnormalities may not be correct. Only careful complete serial physiologic studies can provide the answer to this question.

In summary, 11 of the 15 patients who were rejected for commissurotomy had little or no resting pulmonary hypertension and therefore, in the opinion of the authors, no evidence of significant obstruction at the mitral orifice. In two subjects, left ventricular failure accounted for the pulmonary hypertension. The remaining two subjects with mild hypertension and equivocal manifestations of disability represent a phase of the problem which as yet has not lent itself to definitive analysis.

Patients selected for mitral commissurotomy. Thirty-one patients, including the patient with cured endocarditis who was mentioned above, were deemed suitable for operation after catheterization studies. Three of these refused surgery and another was ultimately rejected because he had a huge aneurysmal left atrium, which in the presence of atrial fibrillation was almost certain to be very thin walled and to contain large thrombi. Surgery was not advised in his case, because the mechanical performance of the commissurotomy would be unusually hazardous. None of these last four will be considered further. The diagnoses and data of the 27 subjects who were operated upon will be found in table 2. The diagnoses in all these patients were made according to criteria previously discussed.[14]

A few general comments are necessary before presenting the results obtained in the 27 subjects who had mitral surgery (table 2).

TABLE 3.—*Physiologic Data in 17 Patients with Rheumatic Mitral Stenosis Selected for Mitral Commissurotomy*

Case Sex, Age	Diagnosis	Time		Card. Output (L/min.)	Card. Index (L/min./M² BSA)	Heart Rate (beats/min.)	O_2 Consump. (cc/min./M² BSA)	R.Q.	A.V. diff. (vol. %)	Arter. blood O_2 cont. (vol. %)	Arter. blood O_2 sat. (%)	Pressures in mm. Hg. System. Art. s/d, m	Pressures in mm. Hg. Pulmon. Art. s/d, m	Pressures in mm. Hg. Rt. Vent. d.	TBV (cc/M² BSA)	PV (cc/M² BSA)	H'crit. (%)
Normal				3.12	72	131	0.80	4.2		96	120/70, 90	30/10, 15	5	2750	1500	45
#659. EB. F. 46 yrs.	EH. MS. (G-S) NSR. IIC.	Pre-op.	(R)	3.22	2.04	97	129	0.86	6.3	16.0	93	119/57, 78	115/44, 70	4	3011	1611	45
#633. GS. M. 28 yrs.	EH. MS. I.AV.B. NST. IIIC.	Pre-op.	(R)	5.69	3.23	102	159	0.76	4.9	15.1	82	92/58, 70	70/38, 55	1	3080	1698	45
			(E)	5.51	3.13	110	197	0.80	6.3	15.0	84	106/66, 79	91/48, 64	5	—	—	—
		Post-op.															
	(T.I.) AF.	9 months	(R)	3.78	2.14	71	143	0.75	6.7	19.7	98	108/68, 83	38/18, 25	4	—	—	—
#744. LD. F. 29 yrs.	EH. MS. NSR. IIIC.	Pre-op.															
		1st Study	(R)	—	—	85	—	—	—	—	—	—	109/50, 79	8	—	—	—
		10 days later	(R)	—	—	93	—	—	—	—	—	—	126/59, 90	8	—	—	—
#722. IK. F. 32 yrs.	EH. MS. NSR. IIC.	Pre-op.	(R)	3.22	2.08	59	116	0.85	5.6	17.7	94	123/65, 88	37/15, 25	2	2610	1458	44
			(E)	—	—	92	—	—	—	—	—	128/67, 90	54/21, 36	4	—	—	—
		Post-op.															
		5 weeks	(R)	—	—	55	—	—	—	—	—	127/63, 88	34/13, 24	—	2703	1620	42
			(E)	—	—	68	—	—	—	—	—	137/66, 93	51/19, 35	—	—	—	—
		14 months	(R)	6.96	4.32	62	134	0.73	3.1	15.6	94	123/63, 88	31/10, 20	—	2850	1772	38
			(E)	7.52	4.67	90	191	1.03	4.1	16.1	95	146/80, 107	61/25, 44	—	—	—	—
#792. MH. F. 41 yrs.	EH. MS. AF. IIIC.	Pre-op.	(R)	2.38	1.76	88	113	0.84	6.6	17.2	94	115/71, 87	70/39, 54	7	2298	1430	38
		Post-op.															
		6 months	(R)	3.06	2.14	64	105	0.79	4.9	17.2	96	122/73, 91	37/20, 26	—	2330	1359	42
#664. JZ. M. 26 yrs.	EH. MS. NSR. IIIC.	Pre-op.	(R)	5.86	3.10	96	161	0.77	5.2	17.8	91	112/73, 87	66/32, 43	2	3098	1573	49

	(T.I.) AF.	Post-op.															

	(T.I.) AF.	Post-op.														
		7 months	(R)	4.39	2.34	75	145	0.82	6.2	17.9	93	113/66, 83	62/31, 43	4	2840	1524	46
			(E)	5.10	2.71	84	198	0.79	7.3	17.6	92	134/81, 98	83/38, 58	6	—	—	—
*627. EB.	EH. MS.	Pre-op.	(R)	4.51	2.58	64	126	0.92	4.9	16.9	99	134/68, 94	60/23, 38	8	3048	1783	42
F. 30	(G-S)		(E)	—	—	78	—	—	—	—	—	139/76, 97	82/38, 53	16	—	—	—
yrs.	NSR. IIC.																
		Post-op.															
		2 months	(R)	3.92	2.28	60	116	0.90	5.1	14.4	97	131/70, 88	47/19, 31	14	3290	2057	38
			(E)	4.92	2.86	80	220	0.87	7.7	14.2	96	130/72, 94	70/31, 45	19	—	—	—
		15 months	(R)	3.29	1.86	60	102	0.76	5.5	15.2	98	114/65, 84	55/18, 34	11	2952	1783	40
			(E)	4.95	2.80	80	168	0.84	6.0	15.3	98	116/71, 88	74/24, 43	15	—	—	—
*606. PT.	EH. MS.	Pre-op.	(R)	4.22	2.59	57	129	0.80	5.0	17.4	93	83/52, 63	38/17, 24	2	3650	1933	47
M. 49	MI.* SA.		(E)	4.76	2.92	90	248	0.90	8.5	18.6	93	116/71, 83	76/32, 48	4	—	—	—
yrs.	IIC.																
		Post-op.															
		1 month	(R)	4.10	2.53	60	129	0.79	5.1	15.5	95	105/60, 76	39/16, 24	—	3197	1864	42
			(E)	5.56	3.43	80	240	0.82	7.0	15.5	92	117/69, 84	82/34, 53	—	—	—	—
		12 months	(R)	3.36	2.10	62	134	0.78	6.4	18.3	95	105/64, 78	39/16, 26	—	3420	1790	48
			(E)	4.94	3.09	83	269	0.80	8.7	18.2	93	111/68, 85	76/33, 53	—	—	—	—
*538. GT.	EH. MS.	Pre-op.															
M. 25	MI. SA.	1st Study	(R)	3.94	2.59	82	161	0.89	6.2	16.9	98	110/65, 81	42/21, 29	5	2920	1690	42
yrs.	IIC.	4 months later	(R)	4.14	2.62	57	134	0.76	5.1	15.6	99	133/69, 90	36/16, 24	—	3036	1868	39
			(E)	5.52	3.50	104	308	0.85	8.8	15.7	98	131/78, 94	76/38, 53	—	—	—	—
*649. JW.	EH. MS.	Pre-op.															
M. 42	MI. (T.I.)	1st Study	(R)	2.74	1.36	92	168	0.76	12.3	20.4	94	134/96, 112	96/53, 75	23	4473	2226	55
yrs.	AF. IIIC.	1 month later	(R)	3.06	1.55	84	149	0.81	9.6	20.1	94	127/84, 103	85/43, 59	9	4380	2053	53
		Post-op.															
		1 month	(R)	3.65	1.85	80	143	0.84	7.7	16.8	97	138/90, 105	70/35, 48	8	4120	2374	42
*723. FH.	EH. MS.	Pre-op.															
M. 37	MI.*	1st Study	(R)	2.58	1.56	106	142	0.86	9.1	18.8	91	130/83, 99	87/55, 67	15	3171	1583	50
yrs.	(G-S)	2 weeks later	(R)	3.20	1.98	91	136	0.87	6.9	17.6	96	116/74, 90	68/38, 50	3	2710	1473	46
	NST. IVD																
*751. JD.	EH. MS.	Pre-op.	(R)	3.18	1.87	88	136	0.88	7.3	18.7	95	119/83, 93	36/23, 30	5	3689	2013	45
M. 32	MI.* AF.		(E)	3.67	2.16	166	285	0.85	13.2	18.4	92	139/85, 109	62/39, 51	11	—	—	—
yrs.	IIIC.																
*662. NW.	EH. MS.	Pre-op.	(R)	2.68	1.77	89	117	0.86	6.6	19.6	94	102/68, 83	46/27, 34	2	2917	1299	56
F. 26	TS.*		(E)	2.83	1.87	100	223	0.92	11.9	20.2	93	121/78, 97	62/34, 42	1	—	—	—
yrs.	NSR. IIC.																
*607. CC.	EH. MS.*	Pre-op.	(R)	3.07	2.07	85	130	0.91	6.3	17.9	95	114/80, 94	84/46, 60	3	2420	1340	45
F. 35	(G-S) AF.		(E)	3.64	2.46	120	226	0.88	9.2	17.4	91	131/88, 97	127/62, 85	9	—	—	—
yrs.	IIIC.																

TABLE 3.—*Cont.*

Case Sex, Age	Diagnosis	Time	Card. Output (L/min.)	Card. Index (L/min./ M² BSA)	Heart Rate (beats/ min.)	O_2 Consump. (cc/min./ M² BSA)	R.Q.	A.V. diff. (vol. %)	Arter. blood O_2 cont. (vol. %)	Arter. blood O_2 sat. (%)	Pressures in mm. Hg. System Art. s/d, m	Pressures in mm. Hg. Pulmon. Art. s/d, m	Pressures in mm. Hg. Rt. Vent. d	TBV (cc/M² BSA)	PV (cc/M² BSA)	H'crit. (%)
#622. JB. M. 36 yrs.	EH. MS.* (T.I.) (G-S) AF. IIC.	Pre-op. (R)	3.16	1.96	88	149	0.77	7.6	19.1	90	135/85, 102	105/49, 74	7	3496	1713	51
		(E)	3.33	2.06	122	244	0.81	11.8	19.4	91	152/91, 110	145/66, 97	11	—	—	—
#609. JB. M. 34 yrs.	EH. MS.* NSR. IIID	Pre-op. (R)	2.88	1.83	100	135	0.86	7.4	15.8	94	95/69, 80	108/59, 81	—	2880	1545	46
		(E)	2.74	1.73	142	239	0.99	13.8	17.5	93	105/72, 84	151/83, 108	—	—	—	—
#700. AC. M. 42 yrs.	EH. MS.* (G-S) RBBB. NSR. IIIC. Healed SBE.	Pre-op (R)	2.70	1.62	79	143	0.86	8.8	19.0	94	127/79, 96	125/46, 76	5	4632	2250	51

* = confirmed by necropsy
M² BSA = per square meter of body surface area
R.Q. = respiratory quotient
AV. diff. = arterio-venous oxygen difference
TBV = total blood volume
PV = plasma volume
H'crit = hematocrit
s = systolic
d = diastolic
m = mean
(R) = at rest
(E) = during exercise
EH = enlarged heart
MS = mitral stenosis
MI = mitral insufficiency
AI = aortic insufficiency
TS = tricuspid stenosis
(G-S) = Graham-Steell murmur
(T.I.) = tricuspid insufficiency
NSR = normal sinus rhythm
NST = sinus tachycardia
SA = sinus arrhythmia
AF = atrial fibrillation
APC'S = atrial premature contractions
VPC'S = ventricular premature contractions
I.AV.B. = incomplete AV block (prolonged PR interval)
RBBB = Right bundle branch block
CHF = congestive heart failure
Healed SBE = healed sub-acute bacterial endocarditis

In addition to the disabling symptoms, all patients accepted for surgery had evidence of hemodynamic abnormalities. In the postoperative period every effort was made to restudy the patient hemodynamically in his best possible state, inasmuch as this had been our aim preoperatively. All medications were continued in the postoperative period, although in some instances it was necessary to reduce the dosage of digitalis. Mercurial diuretics were no longer necessary after surgery in the patients with good or excellent results. It should be noted that the surgeons in our group have hesitated to offer precise estimates of orifice size, but in general have felt that the mitral orifice would not admit the tip of the index finger in all the patients with only mitral stenosis and in every one of these, valve fracture was done. In two (cases 606 and 538) of the five patients with mitral stenosis and mitral insufficiency the orifice would just admit the fingertip and these also had commissurotomies, while in the remaining three subjects (cases 649, 723 and 751) the orifices were sufficient patent to permit easy movement of the exploring finger and no further widening was attempted. No physiologic estimation of the area of the mitral orifice was made, inasmuch as the method at present used for this determination is probably of limited value.[15]

A summary of the results of commissurotomy obtained in the 27 patients subjected to surgery appears in table 2. The conclusions regarding the preoperative status and postoperative physiologic results were derived from a consideration of the hemodynamic studies carried out in these patients, details of which appear, as indicated, either in table 1 and 2 of a previous report[12] or in table 3 of this paper. Criteria for evaluation of such hemodynamic changes have been previously discussed.[12] The final clinical impression regarding each patient is listed as the "postoperative clinical result" in table 2 and the terminology used will be clarified and discussed subsequently. A description of the character of the mitral valve found on exploration was supplied by the surgeon and the biopsies and necropsies were evaluated by the pathologist (M. K.)

The first eight subjects in table 2 were considered to have had an excellent postoperative clinical result. This term "excellent" is employed to indicate that after surgery these patients have become asymptomatic at rest, are almost free of symptoms at whatever levels of activity they undertake, and do not consciously limit their efforts. Only one of the eight is not fully employed and this is for psychiatric reasons. These subjects are receiving the same or less cardiac medication than preoperatively and there have been no signs of peripheral or pulmonary congestion postoperatively.

One of the purposes of this study was an examination of the correlation between the postoperative clinical results and the physiologic results and this has proved to be of great interest. It is immediately apparent from table 2 that those patients who had an excellent postoperative clinical result all had moderate to severe resting pulmonary hypertension preoperatively. In these patients the systolic pressures ranged between 38 and 118, diastolics fell between 16 and 44, and mean pressures between 24 and 71 mm. Hg. The level of resting pulmonary hypertension, as well as the height of this pressure during exercise, decreased significantly after commissurotomy in the seven subjects in whom postoperative physiologic measurements were made. Alterations in the level of resting cardiac output were not as striking as those of pulmonary artery pressures, as four showed no change and only two (cases 567 and 713) a rise after surgery. The blood flow increase during exercise was measured in four patients pre- and postoperatively and in only two of them was the rise in blood flow after surgery satisfactory, that is commensurate with the level of exercise achieved. Despite the fact that these patients were considered to have had an excellent clinical result, only one (case 595) could be said to have achieved normal pulmonary artery pressures and even he continued to have a low cardiac output.

The term "good" has been utilized to describe the clinical results of the next five patients in table 2 who claim marked improvement and have no symptoms at rest. Never-

theless they guard against testing their capabilities to the fullest by consciously setting a ceiling to their efforts beyond which they will not go. Below this ceiling however they have no symptoms. In four of these no change in medication has been necessary while the fifth (case 792) no longer requires diuretics.

All five had moderate to severe pulmonary hypertension prior to surgery (tables 2 and 3) of a degree comparable to that found in the previous group and the range in cardiac output was also similar. In one of the five patients (case 744) two studies were made preoperatively, one before and one 10 days later after digitalization. There was no fall in pulmonary hypertension or in the elevated right ventricular end diastolic pressure. Indeed, the level of pulmonary pressure was higher on the second study when the heart rate was slightly faster. This suggests that these elevated pressures reflected mitral block, probably with complicating pulmonary vascular disease. In the four who had postoperative studies there was a fall in resting pulmonary artery pressures. However in two of them the hemodynamics must be discussed further before full interpretation is possible particularly with regard to cardiac output. One of them was a young musician (case 633) who had marked unsaturation of the arterial blood at the time of the preoperative study (table 3) in addition to the other findings, suggesting transitory subclinical pulmonary edema or the temporary opening of intrapulmonary vascular shunts. A normal arterial oxygen saturation was found on the following day. His postoperative course was stormy and atrial fibrillation appeared and is still present. Five months after surgery he began to improve and at six months he returned to work. Nine months after commissurotomy physiologic studies (table 3) revealed the decrease in pulmonary pressures referred to above, but also a lower cardiac output at rest (−34 per cent) as compared to the preoperative level. The arterial blood was fully saturated. A diastolic murmur was audible at the base of the heart and the mitral murmur was unchanged. It is now three and one quarter years since his operation and the patient is able to undertake any activity without symptoms, except sports which he has not attempted. It is difficult to evaluate the physiologic measurements in this man, since first, there was a fall in cardiac output probably associated with his change of cardiac rhythm to atrial fibrillation. Until the exact relationship between a decrease in pulmonary blood flow and pulmonary pressures can be clarified, his decrease in pulmonary hypertension cannot be ascribed solely to relief of mitral block. Furthermore, if pulmonary edema was present at the time of the first study pulmonary hypertension may have been acutely increased, thus temporarily distorting the measurement as an index of the degree of mitral stenosis and/or pulmonary vascular disease and rendering a comparison of pre- and postoperative measurements extraordinarily difficult.

As can be noted in table 3, another subject (case 722) classed as a good result, had a cardiac output which was considerably higher after surgery but which also was well above normal. This woman was very difficult to study as she was nervous and somewhat unstable, and although the usual criteria for a steady state were met during the cardiac output determination, the high value for blood flow may have been due to anxiety; nonetheless in spite of this high value, the pulmonary artery pressures were not higher than preoperatively.

Thus the subjective expression of improvement was substantiated by the physiologic findings in two (cases 663 and 792) of the four subjects classed as good results. In the other two in whom postoperative studies were realized, physiologic evidences of improvement while highly suggestive were not unequivocal.

Three patients (cases 664, 699 and 635) had no change after surgery. By this term is meant that in none was there any relief of symptoms at rest or during effort, and that they continued to show the same signs of pulmonary or peripheral congestion and fatigue as before surgery.

Hemodynamic studies in these patients who were thought clinically to have had no change after operation, confirm the clinical impression of no benefit, since the pulmonary artery pressures did not alter and the resting cardiac

output fell in two of the three. In two of these men (cases 699 and 635), there was mild pulmonary hypertension at rest and, as has been discussed in a previous report,[12] it is now felt that in them the predominant lesion was not a mechanical block, but rather was myocardial insufficiency. The third patient was subjected to mitral commissurotomy on two separate occasions. This man (case 664, tables 2 and 3), a machinist and former wrestler and boxer had symptoms even at rest. Severe pulmonary hypertension, a normal blood flow at rest and arterial blood oxygen unsaturation were found on cardiac catheterization (table 3). Measurements during exercise were not attempted. He had a difficult postoperative course and showed no improvement after surgery. Atrial fibrillation which began in the immediate postoperative period, persisted. No systolic murmur or left heart enlargement became apparent even though the surgeon felt a small regurgitant jet post commissurotomy. A study seven months after the first commissurotomy revealed no alteration in right heart pressures (table 3) and a fall in cardiac output (−25 per cent). Hence it was decided to re-explore the valve. A further opening of the commissures was accomplished at the second operation and still the patient has not shown clinical benefit. Physiologic studies after the second operation could not be carried out as the patient went into pulmonary edema before the catheter was inserted. In this instance the lack of clinical improvement at the seven months study was mirrored in the physiologic evaluation, a fact which strengthened the impression that no real change had occurred after the first commissurotomy. It is very likely that pulmonary vascular changes secondary to mitral stenosis may be a major factor in this man, and may be irreversible. The fall in cardiac output while it may follow the onset of atrial fibrillation, may on the other hand be the result of a decline in myocardial function as well.

In summary, the hemodynamic evaluation in the eight patients who had excellent postoperative results can be said to confirm fully the clinical impression of benefit from surgery. These individuals were in all likelihood suffering from predominantly a mechanical block at the mitral orifice, as has been discussed in a previous report.[12] The hemodynamic findings of the group classed as good were subject to interpretation as far as cardiac output is concerned, but did confirm a good clinical result if the behavior of the pulmonary artery pressures is accepted as a reliable criterion. In the three individuals who had no clinical improvement following commissurotomy, there was physiologic confirmation of this impression.

The remaining 11 of the 27 patients selected for commissurotomy are dead. Six survived surgery for varying periods of time while five were considered to be operative deaths.

The six who survived surgery will be discussed in detail since operative intervention did nothing to improve their status. Furthermore, since it is doubtful now that any had mitral block as their predominant lesion it is important to seek out their major difficulties. The first of these patients who died was the only one who had mitral stenosis without mitral insufficiency (case 627). Chronic congestive failure was her major problem for three years despite digitalization and diuretics. Only the most rigorous medical regime including bedrest for one month relieved her of congestive signs. Nevertheless hemodynamic studies (fig. 1, tables 2 and 3) showed severe pulmonary artery and right ventricular hypertension at rest and during exercise. Studies made two months after surgery revealed some decrease in pulmonary hypertension but a lower cardiac output and a higher right ventricular diastolic pressure at rest than preoperatively. There were no changes in heart murmurs or heart size. The physiologic findings could hardly be interpreted as unequivocal improvement and indeed as soon as she returned to work as a full time waitress chronic congestive failure reappeared. The patient claimed continuing improvement however. A study 15 months after surgery was not encouraging as right heart pressures were again about the same as preoperatively and her cardiac output had fallen considerably (−28 per cent). It was many months before she volunteered that there never had been any improvement. Nevertheless she had given

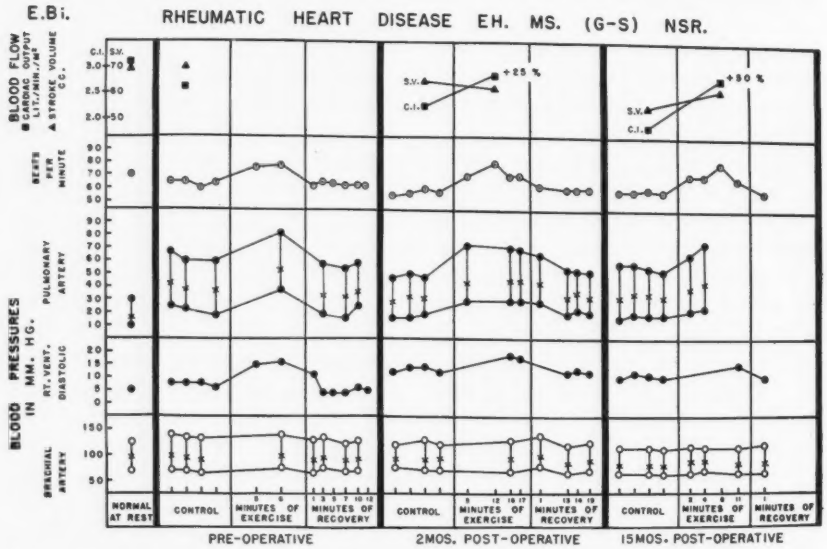

FIG. 1. Graphic representation of hemodynamic findings in case 627, patient E. B. In this, and all subsequent figures, triangles = stroke volume; squares = cardiac index; target dots = heart rate; closed circles = pulmonary artery systolic and diastolic, and right ventricular end diastolic pressures; open circles = brachial artery systolic and diastolic pressures; cross marks = mean pressure. The normal values are plotted in the first vertical column. For discussion see text.

repeated objective proof on physiologic and clinical examinations that her status was steadily worsening. She died suddenly in congestive failure three years after commissurotomy. In view of the continuous fall in cardiac output without lasting fall in right heart pressures, it appears probable that in this woman myocardial damage was of primary concern. Under these circumstances the pulmonary hypertension would be largely the result of left myocardial failure.

In only two (cases 606 and 538) of the five patients with both mitral stenosis and insufficiency was the structure of the valve such as to warrant mitral commissurotomy, since in three (cases 649, 723 and 751) the valve was found to be so insufficient that no fracture was deemed advisable. In all a regurgitant jet could be felt at the time of operation.

Of the two patients in whom valve fracture was done, the first (case 606, fig. 2, tables 2 and 3) had had progressive dyspnea for three years. Studies showed moderate pulmonary hypertension and the surgeon found a deformed valve which he felt was stenotic enough to warrant commissurotomy and the anterior-lateral commissure was cut. Following surgery there was no indication of amelioration as judged from the hemodynamic data. Indeed the cardiac output fell. For 18 months the patient claimed improvement. This, however, he later reluctantly but spontaneously denied. Three and a quarter years after surgery, and after the appearance of atrial fibrillation, he died, following a series of pulmonary infarcts. Throughout his postoperative period there was nothing to suggest an increase in the degree of mitral insufficiency. Surgery obviously had not stayed the course of his disease or improved his hemodynamics, hence it seems likely that much of this patient's difficulty resulted from myocardial insufficiency, even though the valve was greatly deformed and heavily calcified. This conclusion is based on the physiologic observations of a level of pulmonary hypertension which was only moderate and a continuously falling cardiac output. Mitral insufficiency as the main defect appears unlikely since at necropsy the left ventricle showed no gross or microscopic

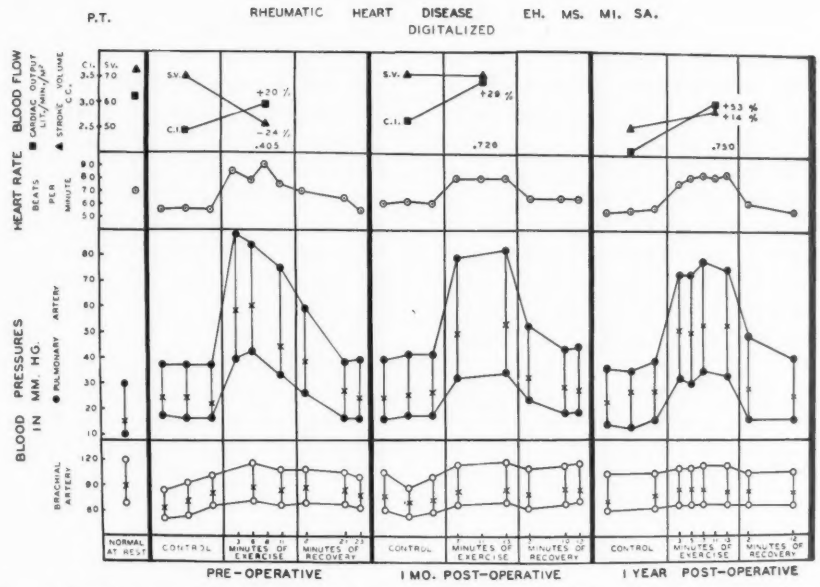

FIG. 2. Graphic representation of hemodynamic findings in case 606, patient P. T. For discussion see text.

evidence of hypertrophy or dilatation. Furthermore, there had been no resealing of the mitral valve, as the orifice at necropsy was just as the surgeon had described it after commissurotomy.

The second man (case 538, tables 2 and 3) had the same basic dysfunction as the patient just discussed but the evidences for myocardial inadequacy appear to have been somewhat more definite. A year of hemoptyses, dyspnea and congestive failure brought this 25 year old patient to the hospital. The response to intravenous Digoxin (fig. 3), characterized by a fall in pulmonary artery as well as right ventricular diastolic pressures and a rise in cardiac output, gave evidence of left ventricular[14] as well as right ventricular failure. Since a second study 4 months later revealed the same level of right heart pressures as after acute digitalization, an element of mitral block could not be excluded, particularly in view of the abnormal exercise response. In the next 10 months this patient's clinical course was unsatisfactory as he continued to have bouts of pulmonary edema and his heart size, as judged by x-ray films, was increasing. For this reason, exploration of the mitral valve was advised although it was recognized that

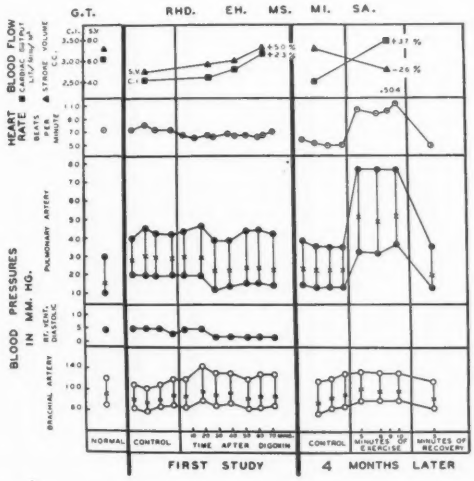

FIG. 3. Graphic representation of hemodynamic findings in case 538, patient G. T. For discussion see text.

there was an element of myocardial insufficiency present. At operation a calcified valve was felt with an orifice approximately the same size as that of the preceding patient's (case 606). The regurgitant jet which could be felt did not diminish after incision of the antero-

lateral commissure. Biopsy of the left auricular appendage revealed evidence of rheumatic activity. The postoperative course was complicated by prolonged low grade fever and 2 bouts of atrial fibrillation. Ten months after operation his heart size was larger than preoperatively, and he was admitted in severe congestive failure and died after the second of two pulmonary infarctions. The final clinical impression was that commissurotomy had not stayed the steady downhill course of active rheumatic heart disease in this young man.

In the remaining three men with a double mitral murmur, the valve was found to be so insufficient that no commissurotomy was attempted. Of these, one (case 649, tables 2 and 3, fig. 4) a former porter, had progressive dyspnea and some intermittent edema for five years as well as occasional hemoptyses. Admitted and subsequently studied while in

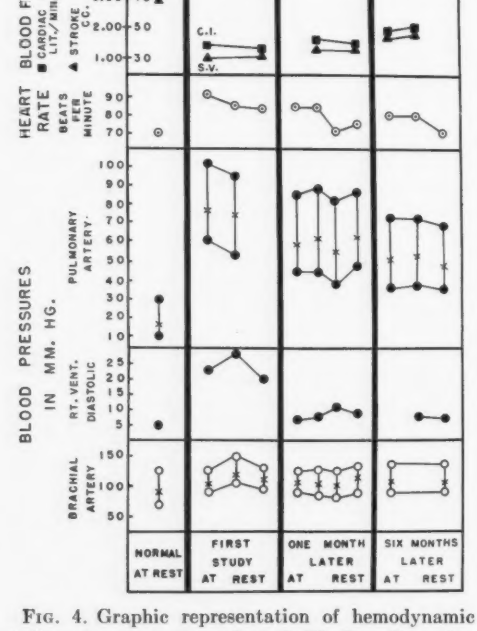

FIG. 4. Graphic representation of hemodynamic findings in case 649, patient J. W. For discussion see text.

congestive failure, he had severe pulmonary and right ventricular hypertension with tricuspid insufficiency and a very low cardiac output. Blood volume was considerably increased. After a month of bedrest, diuretics and continuous digitalis he was much improved, the liver had decreased in size although it was still enlarged, and the lungs were clear. Physiologic studies were repeated (table 3, fig. 4) and although pulmonary artery pressures and blood volume were definitely decreased and cardiac output somewhat increased (+14 per cent), the striking change was a fall in right ventricular diastolic pressure, indicating considerable improvement in right ventricular function. In view of the persistence of pulmonary hypertension it was decided, after another four months of bedrest, to explore the mitral orifice in this man. An opening large enough to admit the index finger readily was found, a regurgitant jet was easily felt and the value edges, which were calcified, failed to close in systole. No attempt was made to fracture or cut the commissures. He had an uncomplicated postoperative course and after one month, a third set of determinations were secured. A further decrease in pulmonary hypertension and a higher cardiac output (+36 per cent), were found while the ventricular diastolic pressure and tricuspid insufficiency were unchanged. These alterations, which incidentally were as large as were found in some of the successful commissurotomies, can be ascribed only to the effects of prolonged medical regime with amelioration in the degree of right and left heart failure, since no change was induced in the mitral valve action. Although nothing had been done surgically to alter his cardio-dynamics, he enthusiastically claimed relief for over two years and returned to work. He was found dead in bed at home two and one half years after operation.

The last two patients with mitral insufficiency and stenosis died in the immediate postoperative period. It appears likely that myocardial insufficiency played a predominant role in their difficulties and in one of these (case 723, tables 2 and 3) this was suspected from the preoperative studies. He was a 37 year old truck driver who had had progressive

dyspnea and orthopnea for two years. At the time of his first study there was clinical evidence of mild pulmonary and peripheral congestion but had severe pulmonary hypertension, a marked increase in right ventricular diastolic pressure with a very low cardiac output. He was digitalized, maintained on strict bedrest and diuretics for the next two weeks. This regime cleared his clinical evidences of congestion. A second study before surgery, showed a considerable drop in all lesser circulation pressures and a 27 per cent rise in cardiac output, all of these indicating decrease in failure not only of the right but also of the left ventricle. There was still, however, a severe degree of residual pulmonary artery hypertension which could have been the result of mitral block and hence it was decided to explore this patient's mitral valve. No commissurotomy was performed as the orifice was approximately 2 fingers in width. He died several days after surgery during uncontrollable atrial fibrillation with a rapid ventricular rate. Necropsy revealed stenosis and insufficiency of the mitral valve without any other valvular lesion. There was hypertrophy and dilatation of the right ventricle and mild dilatation and no hypertrophy of the left ventricle on gross or microscopic examination. It would seem logical to conclude that in this man myocardial failure was an all important factor.

The second subject (case 751, tables 2 and 3) was a 32 year old man with six years of dyspnea. After three months of hospitalization, studies revealed only a moderate resting pulmonary hypertension which became aggravated on exercise, and a very low and relatively fixed cardiac output. Hemodynamically he resembled the two subjects (cases 606 and 538) previously discussed in whom the surgeon attempted valve fracture. However at exploration of the mitral valve in this patient the orifice was large enough to admit over one finger and no fracture was done. Since the orifice was not greatly narrowed he too probably suffered, not from mechanical block, but from inadequate myocardial function. He died four weeks after surgery in congestive failure. Necropsy confirmed the clinical impression as to the valve lesions and further showed that there was mild dilatation and hypertrophy of the left ventricle which contained Aschoff bodies.

Finally, five patients died on the operating table or soon after leaving the operating room. These deaths occurred early in our experience with this surgical procedure. In three (cases 662, 607 and 622) the valve was funnel-shaped and leathery, a finding the surgeon has learned to dread as the leaflets cling to the finger, obstructing blood flow more than usual and resisting fracture. Four of them (cases 607, 622, 609 and 700) were the most severely handicapped of the entire group of 60 studied, as their hemodynamics indicated (tables 2 and 3). Pulmonary hypertension was extreme and cardiac output very low. The fifth (case 662) was less incapacitated, and although her output was also reduced, pulmonary hypertension was only moderate. Uncontrollable hemorrhage from a rent in a very thin-walled left atrium was the cause of death in one (case 609). Cardiac arrest during finger fracture and death within 24 hours due to cerebral damage, occurred in two cases (cases 607 and 662). Cardiac arrest during anesthesia without successful restoration of rhythm by cardiac massage accounted for the death of a fourth patient (case 700). Although the surgical procedure was apparently without incident in the fifth subject (case 622), he did not awaken from anesthesia and died in shock in the eighth postoperative hour.

A review of the auricular biopsy material as given in table 2 indicates that there is little correlation between the presence or absence of Aschoff bodies in the appendage biopsy and the final result after surgery, a point which has been made previously in other reports.[16, 17] Of the 10 patients who survived surgery and had Aschoff bodies in the auricular appendage six developed the postcommissurotomy syndrome. Two suffered from this syndrome who did not have evidence of rheumatic activity as judged from the appendage biopsy. The occurrence of this syndrome bore no relationship to the ultimate surgical result.

Several interesting facts are apparent upon scrutiny of the final clinical result of surgery

and the character of the mitral valve in each case. One should note here that the surgeon's description of the valve as regards shape and character was found to be remarkably accurate whenever postmortem findings were available for comparison. Indeed from such data we have learned that in general a discoid calcified valve, although it can be fractured, may not be associated with a good physiologic result. Furthermore this type of valve is very likely to be grossly insufficient. It should be stressed, however, that the mere presence of calcium in the valve is not important. It is heavy plaques which so distort anatomy and function, that surgical correction at present is not feasible. Diffuse speckling or calcification limited to the orifice on the other hand do permit a good result. The valve which is leathery and funnel-shaped may be impossible to fracture with the finger and unfortunately if the appendage base is narrow, a knife cannot always be introduced to cut the commissure. In general the best hemodynamic result is obtained with a conical shaped mitral valve where the leaflets are supple and calcium or fibrosis, if present, are limited to a ring at the orifice.

Discussion

Before presenting some of the many problems which this study has re-emphasized concerning the patient with rheumatic heart disease and mitral stenosis, a brief recapitulation of the results just presented is in order. Of the 60 subjects referred to this clinic as possible candidates for mitral surgery less than half (27 patients or 45 per cent) were selected for operation. Of these 27 only 13, or 50 per cent had a good or excellent result. In retrospect and as a result of this study we now believe only 19 instead of 27 should have had surgery as, in addition to the 13 good results, we still would select the five patients who were operative deaths since effective fracture had been done in such patients subsequently (cases 703, 659 and 744). Also we would still offer surgery to patient case 664 although he had two unsuccessful attempts at fracture, since, unfortunately even in retrospect, we cannot differentiate him clinically or physiologically from the group with good operative results.

As a result of information gained in this study we would now reject eight subjects who originally were advised to undergo surgery. Two of these (cases 699 and 635) could not definitely be rejected on clinical grounds but physiologic studies[12] would label them as suffering from myocardial insufficiency. In a third (case 627) congestive heart failure required such a rigid medical regime, including constant bedrest for control, that myocardial insufficiency might have been suspected preoperatively. We have learned from the remaining five subjects (cases 606, 538, 649, 723 and 751) that one cannot expect a successful commissurotomy when the murmur of mitral insufficiency coexists with a heavily calcified valve, which calcium could be clearly seen by fluoroscopy in each of these patients preoperatively. In these five also, myocardial dysfunction appeared to predominate. It is well to point out with regard to this state of myocardial insufficiency (as described previously[12]) that it may exist in the absence of enlargement of the left ventricle as judged by gross or microscopic examination as well as by clinical evaluation. Indeed this state may occur without any discernible evidence of pathologic abnormality in the left ventricle, at least as shown by present day methods. It may be that studies of myocardial metabolism will afford a solution to this problem.

Obviously this small group of patients followed through mitral surgery must be observed for a considerably longer time before any final conclusions as to the circulatory effects of commissurotomy are warranted. However, a certain amount of valuable information has been secured even now. It is rather discouraging, for example, to find that of the 13 good or excellent results, not one was entirely cured of his dysfunction by physiologic standards. It is true that one man (case 595) was entirely relieved of pulmonary hypertension at rest and during exercise, but his cardiac output did not change and was still below normal. Although the remaining patients did not attain normal resting pulmonary artery pressures they did have marked falls in pulmonary hypertension. These findings are in agreement with those of Ellis and his coworkers.[18] Con-

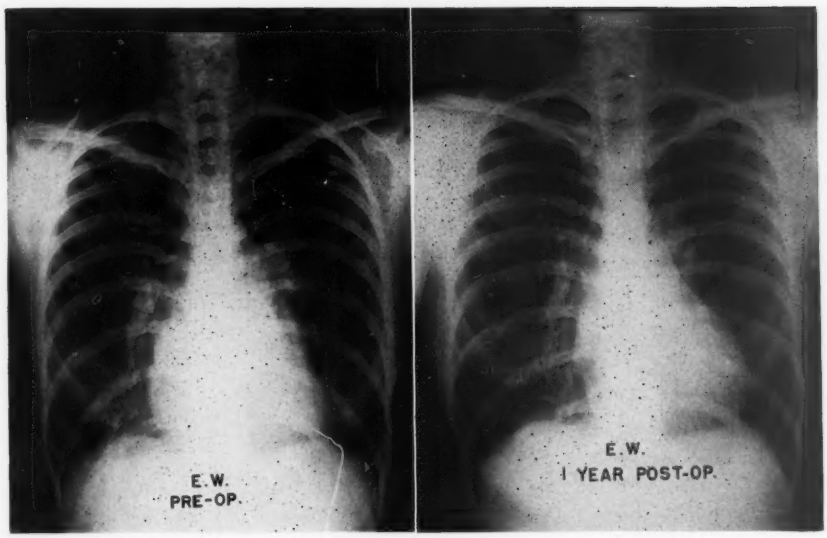

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FIG. 5. Roentgenograms (posteroanterior 6 foot films) of case 713, patient E. W. before and one year after commissurotomy. For discussion see text.

sidering the difficult task which the surgeon faced, namely restoration of valve function in a markedly diseased heart, it is not surprising that he did not always effect a cure.

It is quite interesting to examine the actual level of residual hypertension in those 13 patients who had a satisfactory surgical result. In 9 of the 11 in whom postoperative studies were made, the residual resting pressures in the pulmonary artery (see tables 2 and 3) were surprisingly consistent, averaging 32 mm. Hg systolic, 15 mm. Hg diastolic and 21 mm. Hg mean, with ranges of 23 to 38 systolic, 8 to 20 diastolic and 13 to 26 mean, respectively, although preoperatively the resting levels had varied markedly. It is tempting to speculate on the meaning of this finding of residual hypertension. Is this residual mitral block? If so, it is asymptomatic mitral block. If this pressure elevation is due to pulmonary vascular disease, then the latter must be minimal in 9 of the 11 patients studied postoperatively. It is likely that the remaining two had considerable vascular change as their residual hypertension was severe. There appears to be no way at present to differentiate between these two causes. Perhaps it is simplest to say that we have moved these individuals back a certain distance along the course of the natural history of rheumatic heart disease, but how far and for how long remains to be seen.

Other objective data obtained in the patients before and after surgery are less revealing than the catheterization findings. In only one of the 13 successful commissurotomies (case 713) has there been a decrease in total heart size (fig. 5) although the pulmonary artery segment grew smaller in a number of the subjects. A comparison of pre- and postoperative x-ray films (fig. 6) in one other subject (case 792) emphasizes how little can be the change in cardiac silhouette, with even the double atrial contour along the right border persisting unaltered despite a marked fall in pulmonary artery pressures after surgery. On the other hand, in none was there an increase in heart size once postoperative pericardial effusion had subsided. This latter occurred in 5 of these 13 and took as long as four weeks to recede. In no instance was there any permanent change in heart murmurs, although these became muffled during pericardial effusion. In only one patient (case 713) was there a reversal of the right ventricular

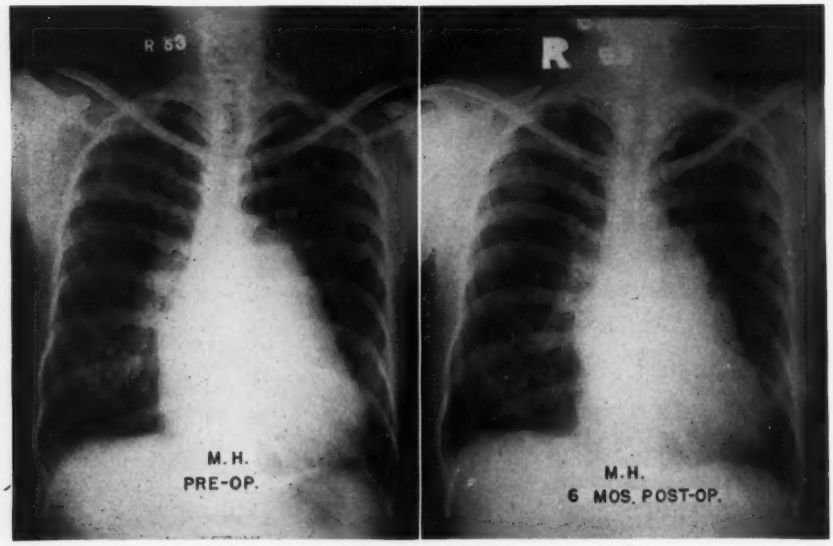

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FIG. 6. Roentgenograms of case 792, patient M. H. before and six months after commissurotomy. For discussion see text.

hypertrophy pattern in the electrocardiogram one year after surgery. Otherwise, the electrocardiographic changes noted preoperatively persisted postoperatively, once the alterations imposed by the acute pericarditis, which all patients developed, had disappeared.

It appears, therefore, from this study that objective physiologic criteria are the most satisfactory in evaluating success in commissurotomy and that one must rely on these rather than on the exclusive use of subjective impressions. This is in agreement with a recent report of Soloff and Zatuchni[19] and could not be better demonstrated than in our own two subjects (cases 627 and 606) in whom the ultimate result was unsatisfactory and in one (case 649) who had no valve fracture, all of whom claimed subjective improvement.

This same expression of subjective improvement forms the basis for the majority of the clinical reports of large groups of patients undergoing surgery. From such reports one cannot escape the conclusion that the clinical criteria utilized have failed to pinpoint the problem and aside from a demonstration that the cardiac can survive this type of surgery, little that is fundamental has accrued to our knowledge of mitral stenosis and its susceptibility to surgery. Even those reports in which objective physiologic data are available, and these are very few in the present literature, have not yet provided us with the answer of how to select the mitral subject who will invariably benefit from commissurotomy. It is therefore obvious that much more study is needed in order to clarify some of the many problems relating to the patient with mitral stenosis.

Selection of patients for commissurotomy. In any consideration of mitral stenosis, and particularly when selecting candidates for surgery, it has become clear from this study that each patient must be evaluated within the framework of rheumatic heart disease itself. For this reason a simple working schema (fig. 7) has been constructed. The effects of the rheumatic process on the heart can be divided into valvular and myocardial. In patients with mitral stenosis however, there may be great variations in the degree of valve deformation and the mere auscultatory diagnosis does not imply a deranged circulation. Hence there exists a group of individuals with stenosis but without significant mitral block in whom

hemodynamic measurements indicate a normal circulation. It is difficult to justify operation on such patients.

Another group of rheumatic subjects who also had predominantly valvular damage are those with mitral stenosis and a significant degree of block. These individuals can go in and out of myocardial congestive failure due to mechanical strain and not myocarditis as shown by the arrows in the schema (fig. 7). These individuals obviously represent the ideal candidates for commissurotomy, particularly if they do have a relatively unimpaired myocardium.

Lastly there is a group of subjects with rheumatic mitral stenosis in whom it has been shown[12] that myocardial damage is dominant and in whom there may be no significant block. The myocardial insufficiency of these hypodynamic hearts will not be benefitted by surgery and indeed such patients may succumb to the operative procedure.

Two of the three types of patients included in this schema, even though clinical evaluation may be difficult, can be differentiated by physiologic studies. The normal circulation of the one and the hypodynamic characteristics of the myocardial dysfunction of the other permit their clear-cut separation on physiologic grounds from the patient with predominantly mitral block.

It is obviously the patient with mitral stenosis and block who is the ideal candidate for surgery, and furthermore, if indeed there is true obstruction at the valve, the patient will have moderate to severe resting pulmonary hypertension. It would perhaps even be advisable to make the establishment of such pulmonary hypertension a prerequisite to acceptance for surgery. In its absence there is little likelihood of the existence of an important degree of mitral block amenable to, or one which will benefit from, surgery.

The selection of the patient might then appear superficially simple, i.e., if there are progressive symptoms, the murmur of mitral stenosis, no clinical contraindications and pulmonary hypertension he would seem to be a proper candidate. This assumes of course that the pulmonary hypertension is not due to left

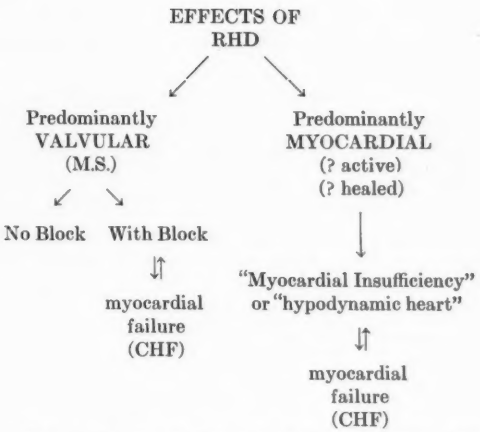

FIG. 7. Schema of Rheumatic Heart Disease. For discussion see text.

heart failure. As a final point, one is faced essentially with determining in any one patient with mitral stenosis whether there is pulmonary hypertension or not, once left heart failure, if present, is relieved. Unfortunately there is no good clinical means of doing this in all instances. Heart sounds or intensity of murmurs do not help, the second pulmonic sound particularly offers no reliable indication and heart size is very deceptive as can be seen in previous reports.[14, 20] Our group is unable to make this determination with certainty unless the patient is catheterized and the pulmonary artery pressures are measured directly. Because the tendency at present is to infer rather than demonstrate pulmonary hypertension, its presence may be improperly diagnosed and hence patients are undergoing needless surgery. This is so because the clinical criteria are as yet grossly insufficient to enable one to choose the correct subjects for commissurotomy. It is true that the ideal candidate can be suspected if there is a small heart, electrocardiographic evidence of right ventricular hypertrophy in the precordial leads and no heart failure, and it is also true that one should beware of offering surgery as amelioration to the patient with a very large heart. These points, however, offer only indirect evidence and in the case of the hypertrophy pattern surely indicate an advanced stage of mitral block.

The fact that no real effort is now being

made in most clinics to establish the presence of pulmonary hypertension in the candidate for mitral surgery may also provide an explanation for some of the unsuccessful commissurotomies reported by some groups; the figures vary between 30 per cent and 40 per cent. In the authors' opinion, the lack of success probably lies in the fact that some patients' very real symptoms were attributed to mitral block when indeed they sprang from myocardial insufficiency. Physiologic studies might have indicated this difference in the etiology of the dysfunction had they been performed. Of course, inoperable valve deformity also is a contributing factor to failure of surgery.

It would therefore seem imperative to continue a combined clinical and physiologic study of mitral stenosis until such time as the reliable clinical signs of obstructive pulmonary hypertension can be ascertained and clarified, thus eliminating the need for cardiac catheterization. The need for such a study is even more apparent when one realizes that the hemodynamic picture of "early" mitral block, i.e. the circulatory state wherein critical narrowing of the orifice is just beginning and the valve is still relatively mobile, remains to be defined. It is probable that once this picture has been critically and physiologically defined, these patients with early mitral obstruction will be the best candidates for commissurotomy.

Summary and Conclusions

This paper presents a study of 60 patients who were referred to this clinic as suitable candidates for mitral commissurotomy.

Of these 60 patients, 15 were deemed unsuitable after clinical study alone; 10 proved to have active rheumatic carditis and five subacute bacterial endocarditis. Another 15 were rejected as candidates for operation after physiologic study; 11 of these had little or no resting pulmonary artery hypertension, two gave evidence that left ventricular failure accounted for the pulmonary hypertension found, while two without disabling symptoms had only mild pulmonary hypertension and represent a phase of the problem which has not as yet been clearly defined. Thirty-one patients were considered suitable for surgery after physiologic studies; of these three eventually refused commissurotomy and one was rejected because of an aneurysmal left atrium.

Of the 27 subjects who underwent surgery, eight were believed to have had clinical and physiologic evidence of an excellent result while five were designated as good results. Nine patients showed no clinical or physiologic evidence of any improvement, and of these, six are now dead. The remaining five were operative deaths.

As a result of this study we would now reject eight subjects who were originally advised to undergo surgery, believing that their predominant difficulty was myocardial insufficiency and not valvular disease.

Our experience with the combined lesions of mitral stenosis and insufficiency is somewhat limited but is discouraging. Indeed we have learned from the five patients in this series with a double mitral murmur that one cannot expect a successful commissurotomy when the murmur of mitral insufficiency coexists with a heavily calcified valve.

Clinical criteria appear as yet inadequate for the selection of the proper candidate for mitral commissurotomy, as there is no good clinical means of establishing in every instance the presence of pulmonary hypertension, which remains the best evidence of a significant degree of mitral block.

Objective physiologic measurements represent the best criteria for the effects of surgery as subjective impressions may be unreliable.

Summario in Interlingua

Inter 60 patientes recommendate como candidatos promittente pro commissurotomia mitral, solmente 27—i.e. minus que un medietate—esseva acceptate super le base de examines plus exacte. Ex iste ultime gruppo, solmente 13—i.e. de nove minus que un medietate—monstrava bon resultatos postoperative, non solo secundo le evidentia clinic sed etiam secundo objective mesurationes physiologic. Tal mesurationes es le melior criterios in judicar le effectos operative proque impressiones subjective es frequentemente pauco digne de

onfidentia. Le gruppo operate includeva 8 atientes que hodie esserea rejicite per nos roque lor difficultate predominante esseva sufficientia myocardiac e non blocage mitral. e nunc disponibile criterios clinic es inadequate ro le efficace selection de candidatos pro ommissurotomia mitral. Il existe ancora nulle on medio clinic pro establir in cata caso le resentia o absentia de hypertension pulmonar; e hypertension pulmonar remane le elior indice de un significative grado de locage mitral.

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Factors in the Etiology of Constrictive Pericarditis

By RALPH A. DETERLING, JR., M.D. AND GEORGE H. HUMPHREYS, II, M.D.

Because of uncertainty existing in respect to the etiologic factors in certain cases of constrictive pericarditis, an analysis of 25 proven cases and of additional series from the literature was conducted. It was evident that a fairly consistent clinical syndrome developed, but the factor of myocardial insufficiency deserves as much consideration as actual constriction by the pericardium. The survey supports the belief that the clinical picture of chronic constrictive pericarditis may result from tuberculosis in most cases, at times only by implication. In addition, cases can result from trauma to the chest, rheumatic heart disease and purulent pericarditis.

DESPITE the success of surgical treatment of constrictive pericarditis, its etiology remains obscure in many cases. Although tuberculosis is frequently cited, in many reported cases a meticulous search has failed to reveal any evidence of this disease in the clinical course, at operation, or at autopsy. Recently attention has been directed to a possible relationship to chest trauma, and the possibility that chronic constriction may result from pericarditis associated with rheumatic heart disease has been suggested.

In order to explore these and other factors which may produce constriction, the records of all patients with a diagnosis of pericarditis treated at the Presbyterian Hospital in New York between the years 1930 and 1954 were reviewed.

I. Analysis of All Cases with Pericarditis

A. Definition

Regardless of etiology, there are varying phases of pericarditis. Acute pericarditis of short duration, such as that associated with uremia, often has no serious sequelae. Once this phase has passed, it is difficult to diagnose chronic pericarditis unless physical signs or electrocardiographic changes persist or calcification appears. There may be no accompanying cardiac dysfunction. Qualifying terms such as purulent, traumatic, fibrinous or adherent make precise classification difficult. Accordingly more than 600 records were reviewed from which a group of 416 cases with definite evidence of pericarditis were obtained for analysis.

From the Department of Surgery, College of Physicians and Surgeons, Columbia University, New York, and the Surgical Service of Presbyterian Hospital, New York. Presented at the Second Congress of the International Society of Angiology, in Lisbon, Portugal, on Sept. 20, 1953.

B. Etiology

1. *Cardiac Disease.* One hundred fifty four cases (37 per cent) were associated with cardiac disesae, of which 139 were rheumatic in origin. Most of these revealed an adherent pericardium at autopsy, and in one the terminal clinical picture and the heavy investment of the heart by a thick fibrous pericardium were characteristic of constrictive pericarditis. In three others the clinical syndrome was suggestive of constriction, but since the patients were living, it was difficult to be certain whether myocardial disease or cardiac restriction played the major role.

In addition to rheumatic heart disease, various other cardiovascular diseases were associated with pericarditis. The most important of these was myocardial infarction. Although the specific diagnosis was made in comparatively few, it seems probable that many other patients with coronary occlusion suffered some degree of subsequent pericarditis.

2. *Infection.* There were 127 patients in whom pericarditis was related to infection. The largest number, 59, or 46.5 per cent were the result of pyogenic bacterial activity. In 21 patients the organism was a pneumococcus. A

ide variety of unidentified organisms were esponsible in 31 others, including one case ue to Friedländer bacillus. In seven, the rganism was not identified. In two patients a taphylococcic infection was associated with n empyema of the left chest. Although suppurative pericarditis has been cited as a cause f subsequent cardiac constriction, none of hese patients developed evidence of constrictive pericarditis. One of these has been bserved for 20 years following drainage and irrigation of the pericardial space with Dakin's solution.[42]

Tuberculosis, either suspected or proven, was considered to be the cause in 53 patients, or 41.5 per cent. Of 41 of these patients reviewed by Wood[71] in 1951, six had developed constrictive pericarditis. In subsequent years, there were 12 additional patients with tuberculous pericarditis, and two more had developed constrictive pericarditis. When these eight cases were separated into probable and proven tuberculosis etiology, it was found that there were four in each category. A positive history and proof of active tuberculosis elsewhere in the body was considered valid evidence that the etiology of the constrictive pericarditis was probably tuberculosis. The difficulty in assigning tuberculosis as the cause is exemplified by at least two recorded cases in which a specimen at the time of surgery revealed tubercles, but later at autopsy, no evidence of tuberculosis could be found in the pericardium.[49]

A nonsuppurative form of pericarditis, unassociated with tuberculosis, was encountered in 14 patients, or 11 per cent. In most instances, the physician noted an association with a respiratory tract infection, and considered the pericarditis to be the result of a virus infection. If some of these patients later develop a constrictive syndrome, it is quite evident that proof of etiology would be most difficult in such patients.

Syphilis was stated to be the cause in one additional patient having a pericarditis. An apparent complete recovery followed adequate therapy of the syphilis and no evidence of constriction occurred subsequently.

3. *Inflammatory Origin.* In 10 cases inflammatory reaction was considered the cause of pericarditis. None of these patients had evidence of constriction. In six, a disseminated lupus erythematosus was the cause, and in one, there was periarteritis nodosa. In two, radiotherapy was thought to be the cause, and in one, silicosis was suggested. The latter case is of interest in view of the fact that intrapericardial instillation of asbestos or talc has been a method of treating intractable angina pectoris. None of the surgeons employing these agents has noted constrictive pericarditis, with a follow-up of as long as 14 years.[9, 63]

4. *Malignancy.* In only eight cases of

TABLE 1.—*Classification of All Cases of Pericarditis Diagnosed at Presbyterian Hospital (1930–1954) Total Cases with Specific Diagnosis—416 Cases*

1. Cardiac pathology			154
a. Rheumatic heart disease		[139]	
b. Miscellaneous		[15]	
Hypertensive cardiovascular disease	3		
Cardiac dilatation	2		
Arteriosclerosis	1		
Infarct	6		
Congenital heart	3		
2. Infection			127
Suppurative (not identified)	7		
Pneumococcic	21	[59]	
Friedlander	1		
Other organisms	30		
Tuberculosis suspect	11	[53]	
proven	42		
Nonsuppurative (viral?)		[14]	
Syphilis		[1]	
3. Inflammatory			
Silicosis	1		
Periarteritis nodosa	1		10
Lupus	6		
Radio therapy	2		
4. Malignancy			8
5. Metabolic			
Myxedema	3		
Scleroderma	1		
Uremia	57		63
Hypoproteinemia	1		
Hyperthyroidism	1		
6. Trauma			6
7. Idiopathic			48
Total			416

malignancy involving the chest wall or lung was there a diagnosis of pericarditis. None of these patients had signs of pericardial constriction. However, two patients, not included in this series, died of acute cardiac tamponade due to a rapidly forming pericardial effusion secondary to involvement of the parietal pericardium by a malignant tumor. As is thought to be the case with myocardial infarction, there must have been many more such cases with pericardial involvement. In such instances, the diagnosis of pericarditis is usually not made because the effusion is not of inflammatory origin.

5. *Metabolic Factor.* For want of a better classification, 63 cases have been listed in this category. None of the patients had the constrictive syndrome. The largest group, 57 patients or about 90 per cent, had uremic pericarditis. In three others, myxedema was present. Scleroderma, hypoproteinemia, and hyperthyroidism were present, each in one patient.

6. *Trauma.* Six patients had suffered a serious crushing injury to the chest, with death occurring in two within a short time. The remaining four survived and developed constrictive pericarditis.

7. *Idiopathic Etiology.* In 48 patients, pericarditis had been diagnosed, but no cause could be determined. In 12 of these, the clinical course and findings at autopsy were compatible with this diagnosis. Without a history of tuberculosis, contact with the disease, or evidence at autopsy, a tuberculous origin could not be assumed. In some, the skin test for the diagnosis of tuberculosis was negative.

II. Analysis of Cases with Proven Chronic Constrictive Pericarditis

Of 30 patients with the signs and symptoms of chronic constrictive pericarditis, 25 were confirmed by operation or autopsy, and cultures, as well as gross and microscopic examination of the pericardium were performed

TABLE 2.—*Analysis of 25 cases of Constrictive Pericarditis from Presbyterian Hospital, N.Y., N.Y.*

Case	Sex	Age	Race	Dyspnea	Orthopnea	Fever	Cough	Precordial Pain	Elev. V.P.	Ascites	Edema	Pl. Effusion	Cardiac Murmur	Cyanosis	Enl. Heart	Diminished Activity	Calcification of Pericardium	Inverted T Waves	Low Voltage	Axis Deviation	Arrhythmia	Pulse Press. < 35	Resp. > 22	Ceph. Floc.	Albuminuria	Circ. Time	Operation	Biopsy Obtained	Etiology	Status
1	F	41	W	+	–	–	–	–	+	+	–	–	S	–	+	+	+	+	+		–	–	–		–		+		I	†
2	F	20	W	+	–	+	+	+	+	+	+	++	–	+		+		+	–	R	AF	–	+				+		TB	†
3	F	53	W	+	+	+	+	–	+	+	+	++	–	–	+	+	+			R	AF	+	+		–	19	+		I	†
4	F	44	W	+	+	–	–	–	+	+	+	+	–	–	–	+	–					–	–		–		–		TB	†
5	F	42	C	+	+	–	–	–	+	+	+	+	S	–	+	+	–	–	+	L	–	–	+		–		–		RHD	†
6	M	10	C	+	–	+	–	+	+	+	+	–	–	–	–	+	–	+	+	R	–	+	+		+	14	+	++	TB	†
7	M	12	W	–	–	–	–	–	+	+	+	+	S	+	–	+	–	+	+		–	+	–	–	–	19	+	+	I	†
8	F	36	W	+	+	+	+	–	+	+	+	–	S	–	+	+	–	–	+		AF	–			–	17	+	+	TB	†
9	F	27	C	+	+	–	–	+	+	+	+	–	–	–							–		+				–		I	†
10	M	40	W	+	–	+	–	–	+	+	+	–	S	–	–		+	–	+		AF	–	–	–		24	+	+	I	•
11	M	43	W	+	+	+	–	+	+	+	+	–	–	–	+	+	+	+	+		AF	+	–	++	+	88	+	+	TR	†
12	F	43	W	+	–	–	–	+	+	+	+	–	–	–	+	–	+	+	+		–	+	–		–		+	+	TB	•
13	M	22	W	+	+	–	–	–	+	+	+	–	–	–	+	+	–	+	+		–	+	–		–		+	+	I	•
14	M	48	W	+	+	+	–	–	+	+	+	++	–	–	+	+	–	+	+		–	+	–	–	–	45	+	+	TR	•
15	M	55	W	+	+	+	+	–	+	+	+	–	S	–	+	+	–	+	+		LBBB	–	+		++++		+		TR	†
16	M	56	W	–	–	+	–	–	+	+	+	–	S	–	–	+	+	+	+		AF	–	–	–	+++		+		I	†
17	M	57	W	+	+	+	+	–	+	+	+	++	S/D	–	–	+	–	+	+		–	+	+	–	–	10	+	++	TB	•
18	M	30	W	+	+	+	–	–	+	+	+	++	–	–	–	+	–	+	+		–		+	–	–	14	+	+	TR	†
19	F	25	W	+	+	+	–	–	+	+	–	–	S/D	–	+	–	–	+	+		–	+	–	++++	–		+	+	TB	•
20	M	50	C	+	–	+	–	–	+	+	–	–		–	–	+	+	+	+		AF	+	–	–	++		+	+	TB	•
21	M	30	W	+	–	–	–	–	+	–	–				–	+	+	+	+			+			–		+	+	I	•
22	M	28	W	–			–	+	+	–					+	–	+	+	+	R		+			–		+	+	I	•
23	M	49	W	+	+	–	+	–	+	+	+	–		–	+	–	+	+	+		–	+	+	–	++	29	+	+	I	†
24	M	38	W	+	–	–	–	+	+	+	–	–		–	–	+	+	–	+		–	+	–	–	–	28	+	+	I	•
25	M	12	W	+	+	+	+	–	+	+	+	++		–	+	–	–	–	+		–		+				+	+	I	†

* Alive. † Expired. ‡ Biopsy positive for tuberculosis.

S systolic
D diastolic
AF auricular fibrillation
LBBB left bundle branch block
R right
L left
I idiopathic
TB tuberculosis
RHD rheumatic heart disease
TR trauma

(Table 2). These 25 patients will be used for the analysis.

A. Clinical Aspects

1. *Sex and age.* There were 9 female patients and 16 males in the series. The age varied between 10 and 63 years, the average being 35.44 years. There were three patients, all male, who were less than 20 years of age; being 12, 12 and 10, respectively.

2. *Signs and symptoms, and their duration* (*Table 3*). Among the 25 cases, an elevation in venous pressure as measured in an antecubital vein was observed in all. In 20 cases in which specific venous pressures were recorded, the range was from 170 to 350 mm. H_2O. It was below 200 in only one patient and the average was slightly above 260 for the group. Following operation, there was a marked fall in all but one case. The pressure then ranged between 65 and 170 mm. H_2O, with an average of about 120. Ascites was noted clinically in all but one patient, and actually may have been present. Edema of the lower extremities, associated at times with presacral edema, was recorded in 19 cases. Contrary to what was expected an enlargement of the heart was noted 11 times by physical examination, and subsequent radiographic study revealed enlargement in two additional cases. Cardiac murmurs were heard in nine cases, there being a systolic murmur in all of these, and a diastolic murmur in two. Pleural effusion was present in nine cases, and was bilateral in two-thirds of them. A friction rub was noted in three patients, and mild cyanosis in two.

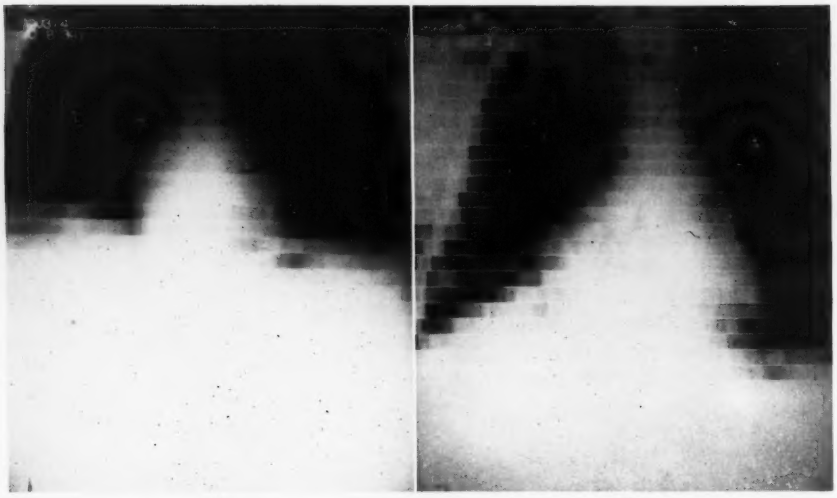
There were 23 patients in whom radiographic studies were reported. These included standard roentgenograms of the chest, and in some instances fluoroscopy, kymography, and angiocardiography. In the two meter frontal roentgenogram, an increase in the transverse diameter of the heart was noted in 13 patients. Diminished heart action was noted by kymography or fluoroscopy in 18 cases (fig. 1). Calcification of the pericardium was recorded in 11 cases (fig. 2). In a few patients, tomography demonstrated calcification of the pericardium when it was not evident in a standard frontal film (fig. 3). It is of interest that the pulse pressure varied between 18 and 60 mm. Hg, and in many it was over 30. There was no correlation of calcification to degree of heart activity or level of the pulse pressure.

TABLE 3. *Symptoms and Signs Associated with Constrictive Pericarditis*

	Cases	Per Cent
Symptoms (25 cases)		
Dyspnea	22	88
Orthopnea	14	56
Fever	14	56
Cough	7	28
Precordial pain	6	24
Signs (25 cases)		
Elevated ven. press.	25	100
Ascites	24	96
Edema	19	76
Enlarged heart	11	46
Pleural eff.	9	36
Cardiac murmur	9	36
Auric. fib.	7	28
Friction rub	3	12
Cyanosis	2	8
Roentgen. findings (23 cases)		
Diminished activity	18	78
Enlarged heart	13	56.5
Calcification	11	48
ECG findings (22 cases)		
Low voltage	21	95.5
Inverted T waves	17	77.5
Pulse rate above 85	9	41
Arrhythmia	8	36.5
Axis deviation	5	22.7
Vital signs (22 cases)		
Pulse pressure <35 mm. Hg	14	63.5
Respirations >22	10	46.5

In 22 cases, additional observations were recorded. The electrocardiogram revealed some abnormality of the T wave in all instances, with inversion in 17 and flattening in 5. Low voltage was noted 21 times. Auricular fibrillation was present in seven cases and bundle branch block in one. A heart rate above 85 beats per minute was present in nine patients. Axis deviation occurred in five cases, being to the right in four.

There was a systolic arterial pressure above 115 mm. Hg in eight patients, but in no case was there hypertension. In 14 patients, the diastolic pressure was below 80 mm. Hg. The pulse pressure ranged from 15 to 50 mm. Hg, averaging about 35 mm. Hg. Respira-



A *B*

FIG. 1. Kymograms obtained in a patient with idiopathic constrictive pericarditis (case 10). *A*. Before operation there was a small globular heart with definitely diminished pulsations. *B*. Following pericardiectomy there was an increase in heart size and pulsations.

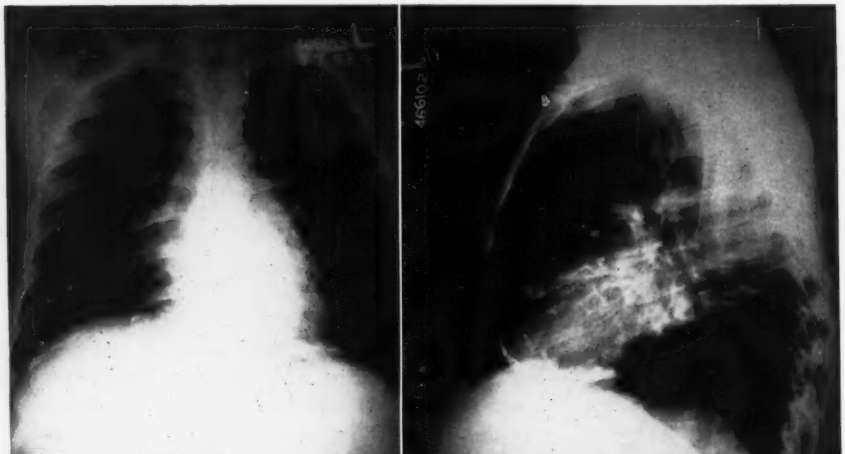
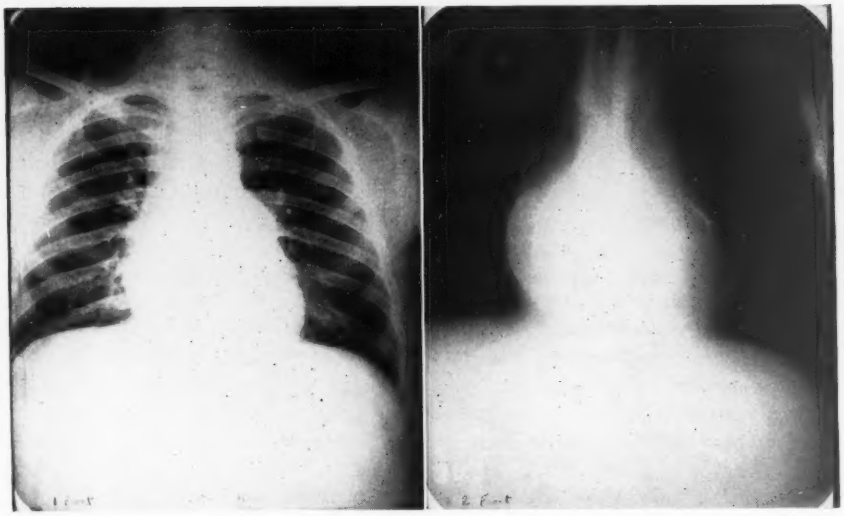


FIG. 2. Roentgenogram in frontal and left lateral projection of a patient with idiopathic constrictive pericarditis, (case 22). Note the calcified pericardium.

tions of more than 22 per minute were present in 10 cases.

The symptoms in all 25 patients varied somewhat, but dyspnea was present in all but two. Orthopnea was noted in 14 cases, and fever had been observed at some time in 14. However, recorded elevation in body temperature was noted in only four cases during hospitalization. Cough was present in seven cases, and precordial pain in six. The duration of symptoms and signs varied greatly, from a few weeks to as long as 25 years. In many cases, the presumptive etiological mechanism preceded evidence of constrictive pericarditis



A B

FIG. 3. *A*. Frontal roentgenogram of case 11 with traumatic constrictive pericarditis which failed to reveal calcium in the pericardium but which is well shown in tomogram, *B*.

by many years, especially in the case of tuberculosis. In general, medical aid was sought within three months of the onset of dyspnea or cough. Ascites of several years' duration was not uncommon. Two patients were actually treated surgically for Laennec's cirrhosis of the liver, with no recognition of constrictive pericarditis for some time subsequently. The cirrhosis was mild by liver biopsy and function tests, yet the clinical course was very poor. The clinicians were puzzled by the progressive clinical deterioration and marked ascites, of a degree much greater than that expected from the cirrhosis. Autopsy revealed chronic constrictive pericarditis, and cardiac as well as portal cirrhosis of the liver in both cases. Tuberculosis was the etiologic factor in one, whereas the other remained idiopathic. In two additional cases of idiopathic constrictive pericarditis, portal cirrhosis was found at autopsy. This is of special interest, since Pick's original paper discussed the differential diagnosis of the two conditions when associated with ascites.[50]

Other laboratory data proved to be of little value. The blood picture was nonspecific. There was anemia in two patients. The white count was elevated in two cases, and depressed in two others. Urinalysis revealed albuminuria in six patients, being severe in only two. The erythrocyte sedimentation rate in 13 cases ranged between 2 and 48 mm. in 1 hour. The average was about 22 mm. in 1 hour.

The serum protein varied between 3.8 and 8.8 Gm. per 100 cu. ml. of blood. There was an average value of 6.64 Gm. in a group of 15 cases. The albumin ranged from 2.1 to 5.5 Gm. and the globulin from 1.6 to 3.8 Gm. In one patient, the globulin equalled the albumin, and in a few others, the normal albumin-globulin ratio was lowered. A nonprotein nitrogen of over 45 mg. per 100 cc. or a serum urea nitrogen of over 30 mg. per 100 cc. was observed in 5 of 17 cases in which this study was performed. The alkaline phosphatase was abnormally high in 7 of 10 cases, but the cephalin flocculation test was positive in only 2 of 11 cases. The circulation time was noted also in 11 patients, varying between 10 and 88 seconds. The average was 28 seconds, but six patients had values of 19 seconds or less. A tuberculin skin test was recorded in only five cases, and was positive in one. This patient had a definite tuberculous constrictive pericarditis, proved at operation and autopsy.

3. *Course and treatment.* The clinical course

TABLE 4.—*A Comparison of Clinical Features in Several Series of Cases*

	Blalock & Burwell[13] 1941	Harrington[25] 1944	Andrews, Pickering & Sellors[2] 1948	Mortensen & Warburg[43] 1948	Paul, Castleman & White[49] 1948	Chambliss et al[16] 1951	Authors 1953
Number of patients	28	24	11	25	53	61	25
Male patients (%)	86	75	55	72	67.9	78.7	64
Age range (yrs.)	14–77		18–63			6–54	10–63
						Av. 31.7	Av. 36.4
Venous pressure elevated (%)	100	100	100	100	92	100	100
Dyspnea (%)	100	64	100	100	78	88.5	88
Ascites (%)	89	79	64	80	60	85.3	96
Edema (%)	96	64	55	76	64	67.2	76
Pleural effusion (%)	86	29	45	56	52.8	—	36
Cyanosis (%)	—	12.5	—	72	30	39.3	8
Albuminuria (%)	24.5	—	—	16	—	—	24
Enlarged heart (%) T.D.	—	25	60	23	54.8	54	56.5
Calcification (%)	—	—	73	48	55	52	48

T.D. refers to transverse diameter of the heart as measured on a frontal two meter roentgenogram of the chest.

of patients with constrictive pericarditis was similar to that of patients with cardiac failure and medical treatment was relatively ineffective as time passed. Most of the cases received digitalis and some diuretic medication. Quinidine was administered to a few, mainly because of auricular fibrillation. As ascites and dyspnea became more of a problem, the clinical condition gradually deteriorated. Prior to 1935, cardiolysis[51], was performed in three cases. One patient with tuberculous pericarditis died at operation, and another with an idiopathic form died on the fifth day following operation. Autopsy of the latter patient revealed pneumonia and portal cirrhosis, in addition to a constrictive, calcified pericardium. The remaining case regained a degree of good health on continued cardiac regimen, and died 12 years later. The cause of her pericarditis remained unknown.

Between 1938 and 1954, pericardiectomy[17] was performed on 18 patients. There were five deaths within a month of operation, and three subsequent deaths between 6 and 18 months from the date of operation. The remaining 10 patients survive, with follow-up as long as 13 years.

4. *Pathology.* Although adherent pericardium does not imply constriction, it was present in all cases of constrictive pericarditis. The pericardium was thickened but generally in an uneven distribution. Often there were fibrous trabeculations into the epicardium and myocardium, and the latter was pale and at times atrophied. The pericardium in some cases measured 5 to 8 mm. in thickness at points of maximal thickness. In some, there was spotty calcification and in others, almost a solid plaque of calcium. In over half the cases, calcium was not noted. A few cases had a cartilaginous-like thickening, with small cystic areas of degeneration. In only four patients was a positive culture for tuberculosis obtained from the specimen, or tubercles found microscopically.

In only a few instances did the pericardium appear as a cast completely encircling the heart. This suggests that with lesser degrees of restriction to heart action, myocardial insufficiency was an additional factor of importance. Indeed, varying degrees of atrophy and muscle damage were noted. In none was there any selective constriction of the cavae or pulmonary veins.

B. Etiology (Table 2)

There were 12 patients in whom no specific etiologic factor could be assigned. Special effort was made to uncover a possible contact or hidden focus of tuberculosis. A negative history and examination was supplemented in four cases by a negative autopsy. In three cases, no autopsy was performed, but there were negative cultures and pericardial specimen

from operation. In one of these there was a negative tuberculin test, as well. Five living patients had negative histories and operative specimens. Two of these also had negative tuberculin tests. With the evidence available, it was difficult to believe the constrictive pericarditis resulted from tuberculosis in seven of the cases, and impossible to prove it so in the others.

Tuberculosis was definitely proved in four cases. In three patients, biopsy and culture were obtained at operation and were positive in only two. Final proof was forthcoming at autopsy in the one case with negative biopsy and in one case not subjected to operation. In an additional four patients, the diagnosis of tuberculous constrictive pericarditis was probable. One patient had a negative specimen at operation, but subsequent autopsy revealed active tuberculosis in mesenteric nodes. Three living patients also had negative operative specimens, but had a past history of proved tuberculosis.

Rheumatic fever had been present 10 years previously in one patient. Her background had been negative for tuberculosis. The clinical picture of constrictive pericarditis developed but operation was not performed. Autopsy revealed no evidence of tuberculosis and minimal valvular damage in the heart. There was significant myocardial damage and a thickened, fibrosed adherent pericardium. It was felt that the pericardial restriction played a definite role in the clinical picture.

Chest trauma was believed to be the underlying cause of constrictive pericarditis in four patients. In three, there had been a steering-post injury at the time of an automobile accident. The fourth patient sustained a football injury. All were males. The clinical picture had developed over a few years in three, but in only eight months in one case. In one case with both epicardial and pericardial calcification a large collection of thick semifluid brownish material, presumably old blood, was present in the pericardial cavity under considerable tension. Two others showed evidence of old blood in the adherent areas. None showed any evidence of tuberculosis in the pericardium removed at operation, and subsequent autopsy in two had failed to reveal any evidence of tuberculosis in the patient. In none was there a history or clinical evidence of tuberculosis.

Discussion

This review of 25 cases of chronic constrictive pericarditis has revealed some features of the disease which apparently differ from the classical concept. These differences may be resolved if we accept the clinical picture of chronic constrictive pericarditis to be a resultant balance between the mechanical restriction of an adherent, unyielding pericardium and the functional inefficiency of a damaged myocardium. It has been shown by Cournand and his group,[28] Moschcowitz,[44] and others that all the salient features of constrictive pericarditis may exist without the "small, quiet heart" described so well by Beck.[7] Certainly, if the pericardial sac thickens throughout and calcifies into a constricting husk within which the heart attempts to function, the classical triad associated with chronic cardiac compression will result.[33] However, with significant myocardial dysfunction, less constriction may suffice to produce the same clinical result. Thus might be explained the observation that the heart may be enlarged.[16, 23, 25, 28, 29, 35, 43, 44, 49, 61] In our own series, this was so in about half the patients. A normal heart action, recorded in about 25 per cent of the group studied by fluoroscopy, and a pulse pressure in excess of 30 mm. Hg, which was observed in many of the patients, strongly suggest that mechanical constriction was not the sole factor in some of the cases. A narrowed pulse pressure (less than 30 mm. Hg) was noted in only 45 per cent of the cases analyzed by Paul and coworkers.[49] Nevertheless, the clinical course and consistent occurrence of elevated venous pressure, ascites, edema and dyspnea, despite careful medical management, suggested that the thickened, adherent pericardium did play a role in addition to myocardial disease. Such a balance might well explain why some patients with tuberculous pericarditis develop the constriction syndrome whereas others do not. It is clear from the literature that only a rare patient has constrictive signs and symptoms

after suppurative or rheumatic pericarditis. It is of further interest that only an occasional case of chest injury later developed the syndrome of constrictive pericarditis.

In view of the fact that our series contained four patients in whom trauma was apparently the etiologic factor, reports of patients who had suffered acute heart injuries were reviewed. It became evident from the reports of Beck,[6] Bigger,[10, 11] Elkin,[21] Kissane,[36] Maguire and Griswold,[39] Naclerio and associates,[45] Ramsdell,[52] Singleton,[59] and Warburg[65] that emphasis was usually placed on technical considerations in management and immediate survival rather than on long-term follow-up. Naclerio and coworkers[45] suggested that failure to perform open exploration of the pericardial space following a penetrating wound might allow pocketing of blood in the posterior-inferior pouches of the space and subsequently produce constrictive pericarditis. Since he and his associates practiced open exploration, they had naturally not encountered any such late sequel. The only traumatic constrictive pericarditis known to him was in a man who sustained a crushing injury to the chest in an automobile accident.[46]

In an effort to determine whether penetrating wound follow-up studies would reveal any instances of chronic constrictive pericarditis, a personal questionnaire was sent to a group of surgeons who have handled many heart wounds. The replies indicated that the follow-up often was very incomplete or uncertain. In one case,[40] localized injury from a penetrating wound and the associated hemopericardium was followed some time later by a constrictive pericarditis. A similar wound in another series produced a tuberculous pericarditis, since the knife passed through a tuberculous area.[53] In 1944 Straus[62] reported the occurrence of constrictive pericarditis in a 46 year old man who had part of a needle left in the heart wall and pericardium at the time of an injection of epinephrine for cardiac resuscitation. No massage was performed. The clinical syndrome developed six years later and was confirmed as constrictive pericarditis by operation. Tuttle[64] has seen two soldiers develop constrictive pericarditis following bullet wounds of the chest, and Mortensen and Warburg[43] reported a case associated with a gunshot wound. Harken,[24] who had extracted many missiles from the region of the heart, had not known of subsequent constrictive pericarditis. Beck,[9] Bigger[12] and Blalock[14] have not observed constrictive pericarditis following penetrating wounds of the heart.

White[69] and other authorities[1, 20, 37, 45] have thought that hemopericardium alone might produce constriction. However, several experimental studies in dogs have failed to support this theory. Fehn in 1913,[54] Beck and Moore in 1925[4] and Ehrenhaft and Taber[20] in 1952 reported their experiments in which instillation of autologous blood within the pericardial cavity of dogs had produced minimal or no adherence and no constrictive signs or symptoms. Ehrenhaft and Taber also injected the lipid fraction of pooled dog blood into the pericardial space of other dogs and typical constrictive syndrome developed at seven weeks in only one animal.

Still, there are many reports of crushing or nonpenetrating chest injury which was followed by constrictive pericarditis. In 1940, Glenn[23] reported the development of constriction three years following a steering-post injury to the chest of a 46 year old man. An autopsy failed to reveal any other possible cause. White and Glendy[68] referred to a patient who developed constrictive pericarditis some time following a chest injury. Dejou[19] in 1946 reported the case of a 19 year old French soldier who had constrictive signs after a nonpenetrating chest injury. In 1948, Mortensen and Warburg[43] in their review made reference to a case of constrictive pericarditis resulting from a crushing injury. Barker and Johnston[3] in 1950, described three cases with constrictive pericarditis, one of whom required pericardiectomy three years following chest trauma. One patient in Blalock's group of cases of constrictive pericarditis had a previous severe crushing injury to the chest.[53] Overholt and associates,[47] in 1952, described constrictive pericarditis occurring in a 50 year old man five years following a nonpenetrating chest injury. No evidence of tuberculosis was noted at operation. Pericardiectomy has also been performed in patients with late traumatic hemo-

pericardium, but without constrictive pericarditis.[1, 20, 37] Harrington[26] and Holman[32] have not observed constrictive pericarditis associated with chest injury.

The possibility that tuberculosis might be the real etiologic agent in some patients with incidental chest injury was raised by Ravitch.[53] He had seen a Negro patient at the time of a penetrating wound of the heart. The patient was treated by repeated pericardial aspiration, which later revealed bloody fluid but not blood. The man had an active apical tuberculosis. It was thought that the wounding instrument went through the focus of infection or nodes. In our series, there was a 10 year old Negro boy who had had chest trauma but in whom the pericardial specimen obtained at the time of pericardiectomy showed tuberculosis. He died at operation, and autopsy further confirmed the diagnosis of tuberculous pericarditis. It is only reasonable that such cases should impress one with the possibility of tuberculosis being the real cause, despite a history of trauma or rheumatic fever. This is especially so, since it is very difficult to demonstrate tuberculosis in the pericardium of patients who very likely have had a tuberculous pericarditis.[13, 66]

Blalock and Burwell,[13] Burwell and Ayer,[15] D'Abreu,[18] Holman,[30, 31] Parsons-Smith and associates,[48] Sellors,[57] Stewart,[61] and others have favored infection (among which tuberculosis ranks first) as the cause of most, if not all cases, of constrictive pericarditis. Many of these authors have rejected the possibility that rheumatic fever could be a competent cause for constrictive pericarditis. Chambliss and coworkers[16] collected 61 cases of constrictive pericarditis among which 10 patients had a previous history of rheumatic fever and no evidence of tuberculosis. They admitted that one of these patients may have developed his constriction as a result of the rheumatic process. Kaltman and colleagues[35] in 1953 reported 18 patients with proved constrictive pericarditis among whom five were believed to have the rheumatic pericarditis as the sole cause. All were males with large hearts. Complete autopsy performed in three failed to suggest other etiology. Calcification of the pericardium was present in only one case. Moschcowitz[44] reported a 25 year old woman believed to have developed constrictive pericarditis on a rheumatic basis. There was a much enlarged heart encased in a very thick, calcified pericardium found at autopsy. Partial pericardiectomy had been performed on two occasions with definite relief each time. Among our cases of proved constrictive pericarditis, there was a 42 year old Negro woman with a course suggestive of this syndrome, in whom there was a rheumatic heart disease. At autopsy, there was an enlarged heart encased in a thickened, adherent pericardium and no evidence of tuberculosis. In addition, there were minimal valvular abnormalities. In our group of five unproved cases there were three patients with only a rheumatic background as a possible cause.

It would be well to reiterate that adherent pericardium should not infer constriction. A review at Massachusetts General Hospital in 1932[60] revealed 43 patients with adherent pericardium among 1900 autopsies or 2.3 per cent. Twenty-two were on a rheumatic basis. There were no constrictive cases among the entire 43 cases. A previous collection of 62 additional cases of adherent pericardium from 3053 autopsies had revealed three cases with true constrictive pericarditis. They were all of proved tuberculous origin. Moschcowitz[44] found 130 cases of adherent pericardium from 9618 autopsies, or 1.4 per cent. Rheumatic pericarditis was the cause for 46.2 per cent of cases with complete or partial adherence. We found 49 cases with adherent pericardium, and rheumatic pericarditis was considered as the cause in 24 instances, or 49.5 per cent. Only one of these 24 patients had constrictive signs and symptoms. In only one case was myocardial infarction thought to be the cause of a constrictive pericarditis.[43]

Polyserositis with indeterminate or atypical endocarditis[38] was claimed by Moschocowitz[44] to be the cause of one proved case of constrictive pericarditis examined at autopsy. Polyserositis as a cause has been listed by other authors, but usually in association with rheumatic heart disease, tuberculosis or pneumonia.

2, 27, 66 Wood and Krumbhaar[70] do not believe that polyserositis alone leads to constriction.

Suppurative pericarditis can produce a constrictive pericarditis but does so infrequently. The reports of Blalock and Burwell,[13] Harrison and White,[27] Johnston and Mangiardi,[34] Shipley and Winslow,[58] and others indicate that the pneumococcus or staphylococcus is the usual organism. We found no constrictive pericarditis developing among our 59 cases of suppurative or pyogenic pericarditis, in 21 of which a pneumococcus was recovered. It is of special interest that the case of streptococcic pericarditis treated by irrigation with fresh Dakin's solution did not develop constrictive pericarditis.[42] Beck[5] reported constrictive pericarditis as a complication of the use of Dakin's solution inside the pericardial cavity.

Since all authors readily accept tuberculosis as a proved cause for chronic constrictive pericarditis, we shall only re-emphasize the fact that it is very difficult to prove the diagnosis in many cases in which presumptive evidence exists. White and Churchill[67] proved tuberculosis to be the agent in only 5 of 37 cases, whereas Blalock and Burwell[13] found 21 tuberculous cases among 28. Harrington[25] reviewed 24 cases and proved tuberculosis in only 5. Sellors,[57] on the other hand, claimed 16 of 20 cases to be tuberculous. Holman[30] reported four proved cases among nine; and McKusick[41] considered 8 of 20 cases to be proved or probable. Stewart[61] proved tuberculous cases among 25. Almost without exception, there are "idiopathic" cases in all series, and it is certain that additional cases of tuberculous pericarditis will be recognized among these when autopsy is performed. It is impossible to implicate virus infection in some of these patients with any assurance, but in the future, more careful study and documentation may produce evidence for or against such an etiologic agent. Harrington,[25] Paul and coworkers,[49] Sellors,[57] and others cite operated cases in which the only positive finding was the history of a previous attack of influenza or atypical pneumonia. In our series, similar cases are classified as idiopathic.

There is a remarkable agreement in the clinical syndrome when our findings are compared with those of several other authors who have carried out detailed analyses (table 4). The high percentage of patients with enlarged heart was quite interesting. Blalock and Burwell[13] indicated that they had encountered no marked cardiac enlargement, but no mention was made of slight increases in transverse diameter. While some of the enlargement observed in certain patients may be the result of the shadow caused by a thickened pericardium, there are many cases in which this is not the sole factor.

In these series there were patients treated for some time with a clinical diagnosis of portal cirrhosis, and the cases of Glenn[23] and of Straus[62] are additional examples. In our series, there were four patients with constrictive pericarditis, in whom portal and cardiac cirrhosis was found at autopsy. Two of these patients had been treated vigorously for portal cirrhosis during several years and had had omentopexy or splenectomy. Liver biopsy had confirmed only moderate portal cirrhosis. However, the poor clinical course and excessive ascites, edema and dyspnea for the degree of liver dysfunction, led to the late suspicion that a cardiac element also existed. This was confirmed at autopsy. Our experience is interesting when one recalls the original paper by Pick,[50] describing pseudocirrhosis in three patients. Although Harrington[25] noted some retention of bromsulfalein in all of his cases, the liver function tests are usually not seriously affected in chronic constrictive pericarditis. Therefore, one must consider possible pericardial disease in a patient with large liver, ascites and fairly good liver function. However, the possibility of both conditions coexisting in a patient cannot be excluded.

Ascites and pleural effusion appear to be the result of an inefficient right heart, as suggested by elevated venous pressure, edema, and occasional cyanosis. We believe this to be the sum of compression and myocardial ineffectiveness. A study of the heart muscle of patients with constrictive pericarditis has revealed actual atrophy of the fibers.[55] When one adds varying degrees of actual myocardial damage from a circulatory or disease process, it may

not require a great amount of actual constriction for the development of the constrictive syndrome. Holman[30, 31] and Lambert[37] have considered constriction of the vena cava to be of real importance in the development of the syndrome. However, Sawyer and associates,[56] Sellors[57] and others have questioned this, and in none of our 11 patients having complete autopsy was there evidence of significant narrowing of the cavae. At least a 50 per cent reduction in cross sectional area of the inferior vena cava is necessary for the production of ascites.[31]

Harvey and coworkers[28] studied five patients by cardiac catheterization during various stages of the clinical course, and found that calcification of the pericardium alone in no way implies constriction, and also that there may be significant myocardial damage in the patient with clinical constrictive pericarditis. In their opinion, this is at times a reversible factor. This analysis[28] indicates that pericardial constriction may not be the sole or even major factor. That patients with significant myocardial damage and minimal pericardial restriction may be headed for fully developed constrictive pericarditis has been suggested in case reports by Lambert[37] and by Moschcowitz.[44]

In conclusion, from this analysis of 25 patients with proven constrictive pericarditis and comparison with cases reported by other authors, certain factors appear to be important in the development of the clinical syndrome of constrictive pericarditis: (1) Prolonged exposure of the pericardium to irritant or damaging agents; tuberculous infection, foreign bodies or partially organizing blood clot are examples. (2) Extensive pericardial involvement rather than discrete localization. (3) A varying degree of pericardial compression or constriction in association with myocardial damage by disease or injury.

Summary

An analysis of 416 cases of pericarditis treated at the Presbyterian Hospital in New York between the years 1930 and 1954 has been presented. From this group, there were five patients with the clinical but unproven diagnosis of chronic constrictive pericarditis, and 25 in whom the diagnosis was proved by operation or autopsy. The signs and symptoms presented by these patients are comparable with those reported by others. There was a high incidence of cardiac enlargement. Investigation of etiologic basis for constrictive pericarditis in this group and in reports by other authors indicated that it is impossible to determine a definite cause in many patients. Among proved causes, tuberculosis is the most frequent. Evidence is presented that injury, purulent infection of the pericardium, and rheumatic heart disease may produce the constrictive syndrome. The concept that this syndrome results from a myocardial factor as well as pericardial compression is emphasized.

Summario in Interlingua

Es presentate un analyse de 416 casos de pericarditis tractate al Hospital Presbyterian de New York inter le annos 1930 e 1954. Le gruppo include le casos de 5 patientes con un non-confirmate diagnose clinic de pericarditis constrictive chronic e 25 casos con le mesme diagnose confirmate al operation o al autopsia. Le signos e symptomas presentate per iste patientes es comparabile con illos reportate per altere autores. Nos trovava inter illes un alte frequentia de allargamento cardiac. Le investigation del base etiologic de pericarditis constrictive—tanto in nostre serie como etiam in illos reportate per alteros—indica que il es frequentemente impossibile determinar un causa specific. Inter le causas demonstrate, tuberculosis es le plus frequente. Nos presenta datos in supporto del conception que le syndrome constrictive pote esser producite per vulneres, infectiones purulente del pericardio, e morbo rheumatic del corde. Nos sublinea le conception que le syndrome pote resultar ab factores myocardiac tanto ben como ab un compression pericardiac.

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Calcification of the Pericardium in Apparently Healthy People

Electrocardiographic Abnormalities Found in Tracings from Apparently Healthy Persons with Calcification of the Pericardium

By F. A. L. Mathewson, M.D.

Case histories are presented of five apparently healthy persons showing pericardial calcification. Calcium deposits form in the dense pericardial scarring which is responsible for changes in the electrocardiogram. Awareness by the cardiologist of the possibility of pericardial scarring makes him particularly alert to electrocardiograms showing normal QRS complexes with T wave changes, particularly if the T waves point in a direction opposite to the main QRS deflection and are associated with RS-T segment depression. Low QRS voltage may or may not be present. Suspicion will be increased in serial records when the abnormalities remain constant over a period of years.

CALCIFICATION of the pericardium is an uncommon condition of uncertain etiology. Calcium deposits do not form in the healthy pericardium but in the dense fibrosis and scarring which may follow pericardial inflammation. Tuberculosis, rheumatic fever, pyogenic infections, and trauma have been named as causative agents, but in many instances the exact nature of the primary lesion remains unknown. The deposition of calcium may continue for many years; long after the active inflammatory process has disappeared. Its presence constitutes strong evidence of diffuse scarring of the pericardium. Hence it is observed in patients presenting the clinical picture of chronic constrictive pericarditis. Harrison,[1] Paul,[2] and Evans[3] reported it in 43, 55 and 70 per cent of their respective series. Pericardial scarring, with or without deposition of calcium salts, is known also to occur in persons showing no evidence of heart disease. Jones[4] reported absence of cardiac symptoms in 9 out of 38 cases of calcified pericardium, while Armstrong[5] at the London Hospital reported no symptoms in 31 of 114 cases showing a completely adherent pericardium at autopsy. That pericardial calcification may occur in apparently healthy individuals has been reported by various observers.[6, 7, 8, 9] It is important then to recognize that pericardial scarring may be present in persons who do or do not show clinical evidence of heart disease and who on radiological examination may or may not exhibit pericardial calcification.

The detection of pericardial scarring in asymptomatic persons rests upon the demonstration by x-ray examination of calcium deposits in the pericardium or the appearance of suggestive changes in the electrocardiogram. It is the purpose of this paper to present the case histories of five apparently healthy individuals who were found to have pericardial calcification and to discuss certain electrocardiographic findings which are thought to be of diagnostic importance.

Case Reports

Case 1. On March 14, 1952 a business executive, age 52, underwent a routine medical examination. He was refused life insurance in 1920 supposedly because of a heart murmur and high blood pressure. In 1950 a gangrenous appendix was removed. There

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Presented at the Second World Congress of Cardiology held in Washington, D. C., Sept. 16, 1954.

This study was supported by grant No. 219 of the Defence Research Board, Department of National Defence, Ottawa, Canada.

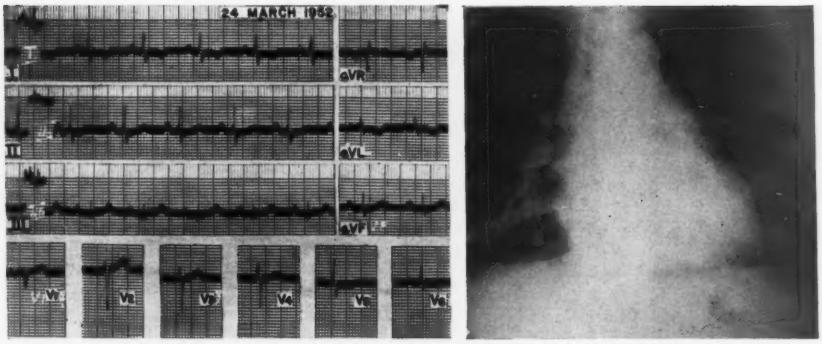

FIG. 1. Case 1. Electrocardiogram and x-ray film of chest at the time of initial examination in 1952.

were no other reported illnesses. His mother died of heart disease at age 52.

The patient's height was 5 feet 7½ inches; weight, 203 pounds, and blood pressure, 150/86 to 144/80. General examination was otherwise normal. An electrocardiogram was recorded on March 24, 1952 and an x-ray film of the chest on April 7, 1952.

In the electrocardiogram (fig. 1) the RS-T segments in leads I and II are depressed and the T waves in lead I are inverted. In precordial leads V_5 and V_6 the RS-T segments are slightly depressed and the T waves are low or inverted. This record was considered to be abnormal but no clinical connotation was suggested. The heart was not enlarged by x-ray examination (fig. 1) and there was no visible calcification.

This man died from accidental causes on April 24, 1952. A postmortem examination carried out by Dr. D. W. Penner revealed a thickened calcified pericardium. Extracts from the autopsy report follow:

Gross findings. Both lungs are adherent to the parietal pleura by old firm adhesions and their roots are firmly adherent to the pericardial sac. The lungs themselves show no gross changes, other than marked congestion and some mucus accumulation in the bronchi.

The pericardial sac is thickened and firmly adherent to the visceral pericardium from which it cannot be separated. The heart (with pericardium) weighs 770 Gm. The valve rings measure: mitral 10 cm., aortic 6 cm., tricuspid 11 cm., and pulmonary 7 cm. The entire parietal pericardium is rather firmly attached to the visceral pericardium, although in areas it can be separated with blunt forceful dissection. The valves are all grossly normal. The wall of the right ventricle measures 5 mm. and the left up to a maximum of 18 mm. The coronary arteries appear relatively small. They are patent throughout and although there is minimal diffuse atheroma present there is no appreciable narrowing of the lumen at any site. Sections of the myocardium

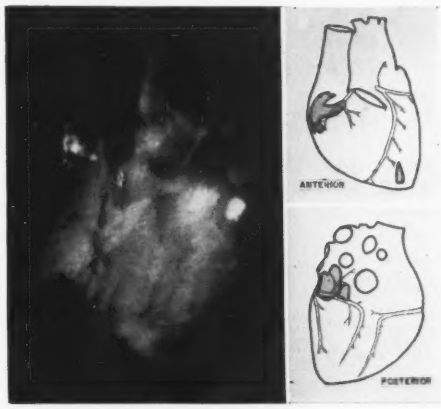

FIG. 2. Case 1. X-ray film of heart after death showing calcified plaques. The location of the plaques are shown in the diagrams to the right.

show no gross evidence of fibrosis. Located in the pericardium are four separate calcareous masses (fig. 2); the largest, measuring 3.5 by 2 by 1.3 cm. lies along the right lateral border of the right auricle. The inferior margin of it overlies the coronary artery which passes deep to it at a point 5 cm. from its origin. The vessel is not attached to the mass. Two similar, but smaller, calcareous masses overlie the course of the left coronary artery in the auricular-ventricular groove on the posterior surface of the heart, just at its left lateral border. These two masses adjacent to one another measure 1.5 cm. and 1 cm. and occur at a point 4 cm. from the origin of the left coronary artery. A fourth small calcareous mass, 3 mm. in diameter, is present at the apex. The gall bladder is normal in size. The lumen contains yellow bile, two mixed 1.2 cm. calculi, together with numerous tiny calculi and biliary mud. The bile ducts are not remarkable.

Microscopic Findings. Myocardium: Old fibrous

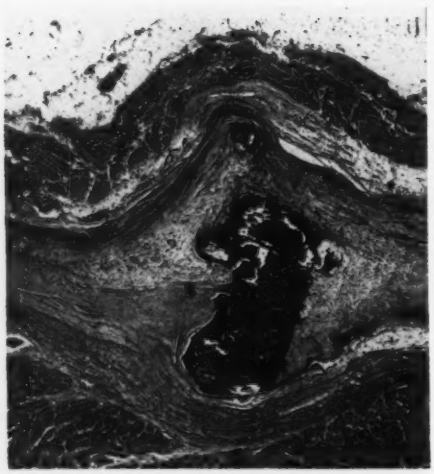

FIG. 3. Case 1. Section showing densely fibrosed pericardium with calcium plaque. The relatively normal myocardium appears below.

adhesive pericarditis is present with areas of calcification and ossification. There is almost no cellular infiltration present, i.e. no evidence of active inflammation. The myocardium shows patchy areas of minimal interstitial fibrosis (fig. 3). The liver shows early portal cirrhosis and some fatty changes.

Summary. Old adhesive pericarditis with calcification and ossification. Early portal cirrhosis.

Case 2. A 32 year old pilot was examined on Jan. 18, 1945 prior to his release from the Royal Canadian Air Force. A routine electrocardiogram at that time was found to be grossly abnormal. This tracing was identical with that of Sept. 20, 1945 which appears in figure 4. Here the RS-T segments are depressed and the T waves are inverted in leads I, II, III and CF4.

Between 1945 and 1954 this man was examined repeatedly because of the persistently abnormal electrocardiogram. At each examination he was found to be in good health and at no time had he symptoms of heart disease. There was no history of rheumatic or scarlet fever. The father, mother and family physician who looked after him from birth could not recall his having had any serious illness. He remained well in the Air Force. Since the war he has been continuously employed by a logging company as woods superintendent.

The family history was normal except that a younger brother had pleurisy during the war and was later treated for pulmonary tuberculosis. He had no contact with this brother. He was married in 1950 and has two children.

On examination he was 70½ inches tall and his weight increased from 149 pounds in 1942 to 175 pounds in 1954. Blood pressure was always within the range of normal (e.g. 122/74). The heart was normal in size and rhythm. A soft apical systolic murmur was heard once in 1945. There were no other noteworthy findings.

The consultant who examined him in 1945 summarized his opinion as follows: "I am unable to explain the unfavorable electrocardiograms. There are no symptoms and no physical signs to suggest heart disease, and there is no history of rheumatic fever, pericarditis, or trauma that could help explain the inverted T waves."

Serial electrocardiograms over the years have been identically abnormal, except for some increase in QRS voltage (fig. 4). Recently this man's heart was examined radiographically specifically for signs of calcification of the pericardium. The films taken on Jan. 12, 1954 are reproduced in figure 5. Extensive calcification of the pericardium is present at the apex of the heart and is seen to extend over its lower anterior surface.

The Department of Veterans Affairs kindly made available the 1942 and 1945 x-ray films taken on entering and leaving the Royal Canadian Air Force. In retrospect calcification can be seen in the 1945 film and with less certainty in the 1942 film.

Case 3. A 49 year old baker underwent a routine medical examination on Dec. 21, 1953. He stated that he was in good health. His father was still living at 85 and his mother died at the age 82. Apart from a history of pleurisy many years ago, there were no other known illnesses. He had received periodic medical examinations for the past three years. These examinations included photoroentgenograms of the chest. The height was 5 feet 5 inches, weight 191 pounds, blood pressure 122/88. Apart from mild varicosities of the right leg, examination was clear.

An electrocardiogram and a single x-ray film of the chest were taken on Feb. 1, 1954 (fig. 6). The electrocardiogram shows left axis deviation with depressed RS-T segments in leads I and II. The T waves are acutely inverted in lead I and low in lead II. The RS-T segments in V_3 to V_6 are depressed and the T waves in V_1 to V_6 are inverted. The x-ray film of the chest clearly shows calcification of the pericardium along the left border of the heart. The right costophrenic angle is obliterated by old adhesions.

Case 4. A 50 year old woman sought medical advice because of palpitation, nausea and a sense of heaviness in the abdomen. On June 7, 1954 during fluoroscopy in connection with an x-ray examination of the gastrointestinal tract, the radiologist observed calcification of the pericardium. She was first seen in January 1949 with hot flushes, mild mental depression and vague joint pains. Examination did not reveal any abnormality and her symptoms were believed due to menopause. Because her basal

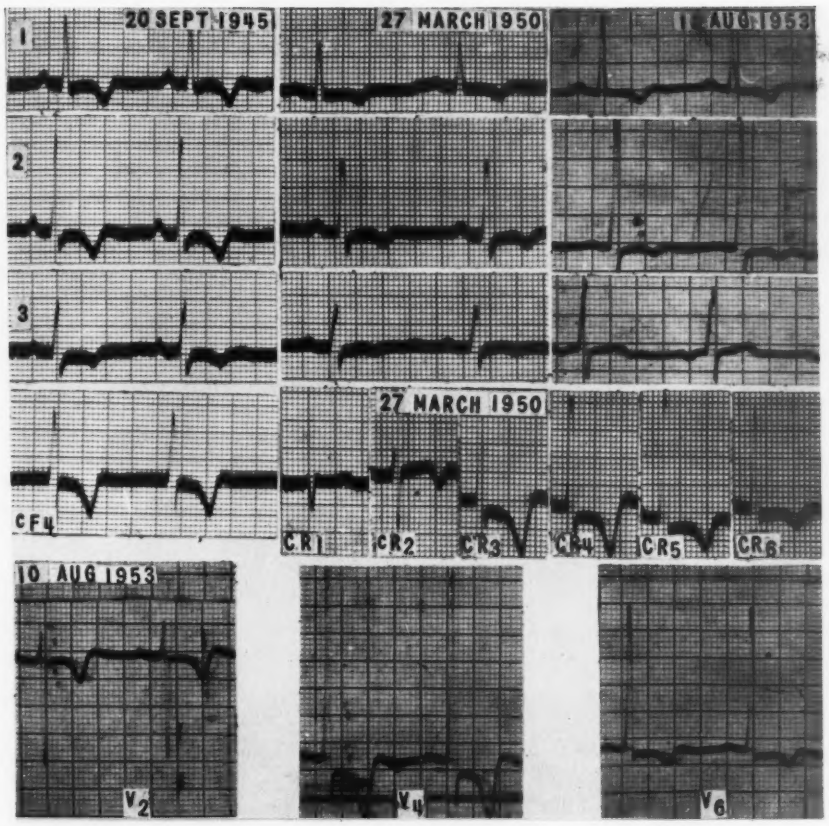

FIG. 4. Case 2. Electrocardiograms recorded in 1945, 1950 and 1953 show RS-T segment depression in lead II and III and in the precordial leads over the left ventricle. The T waves are inverted in all leads. The QRS voltage increased between 1945 and 1953.

metabolic rate was minus 28 per cent, desiccated thyroid gland was prescribed. In September 1950 she consulted her physician because of spells of weakness and perspiration. These responded to symptomatic treatment. Again in June 1953 she complained of palpitation intermittently for a period of two weeks. Nothing was found on examination and she improved with mild sedation. In March and April 1954 there were two further episodes of palpitation. These attacks lasted three hours, one following an emotional upset. The character of the attacks did not suggest paroxysmal tachycardia. There was no history of rheumatic or scarlet fever. On close questioning she admitted noticing dyspnea on exertion for the preceding year. She experienced no distress following her usual sedentary occupation of commercial artist.

The family history was not significant, with the possible exception of a maternal grandmother dying of tuberculosis and the coincidence of two brothers having stones removed from the bladder. The height was 5 feet 10 inches; weight 165 pounds; blood pressure 110/80. A soft pericardial rub, systolic in time was audible in the third intercostal space to the left of the sternum. Apart from some tenderness in the right lower quadrant of the abdomen, examination was normal. The venous pressure in the right antecubital vein was 120 mm. water.

The electrocardiogram (fig. 7) shows a broad P wave in lead II; the T waves are flat in lead II and inverted in lead III. The RS-T segment is depressed in V_6 and the T wave here is flat. The x-ray films of the heart show in the anterior view calcification of the pericardium along the left border and at the apex. It can be seen to extend well up behind the heart in the lateral film (fig. 7).

Case 5. A 64 year old baker superintendent had an x-ray examination of the gastro-intestinal tract on May 31, 1954, and during fluoroscopy, the radiologist observed calcification in the region of the heart.

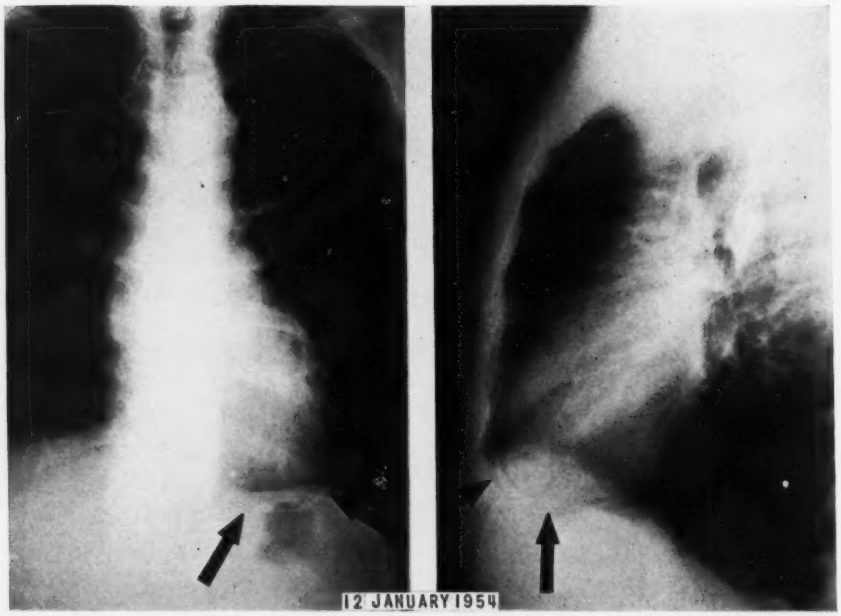

FIG. 5. Case 2. Calcification of the pericardium is clearly visible in both the posteroanterior and lateral films recorded in 1954.

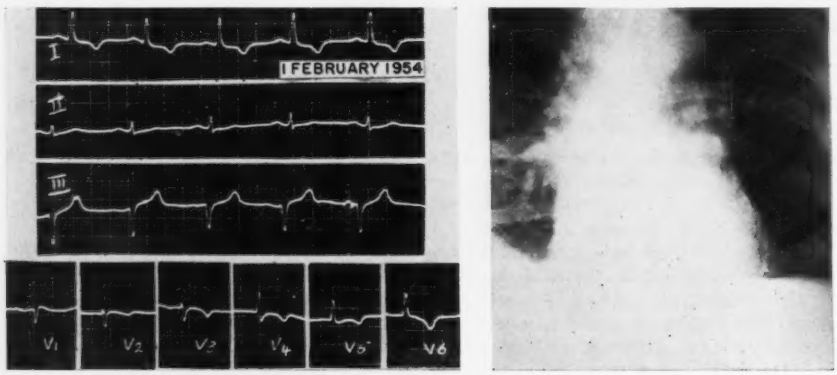

FIG. 6. Case 3. In the electrocardiogram the RS-T segments are depressed in leads I, II and V_4, V_5 and V_6. The T waves are flat or inverted in leads I and II and in all the precordial leads. The x-ray film shows calcification of the pericardium along the left border of the heart.

Recently he had experienced a "lump" high in the epigastrium for which he consulted his physician. This sensation was always present toward the end of the working day but not felt in the evening when working in his garden. He admitted during the past winter having shortness of breath on occasion but it did not interfere with his work which at times was quite heavy.

He was born in Belgium and came to Canada at the age of 39 years. Apart from influenza in 1918 he experienced no serious illnesses. The family history was negative.

The height was 5 feet 6 inches; the weight 141 pounds; the blood pressure 122/74. The veins of the forearms were prominent but there was no cervical engorgement. A soft cardiorespiratory murmur was heard at the apex. Examination was otherwise normal. Venous pressure measured in the right antecubital vein was 180 mm. H_2O.

The electrocardiogram (fig. 8) is normal except for

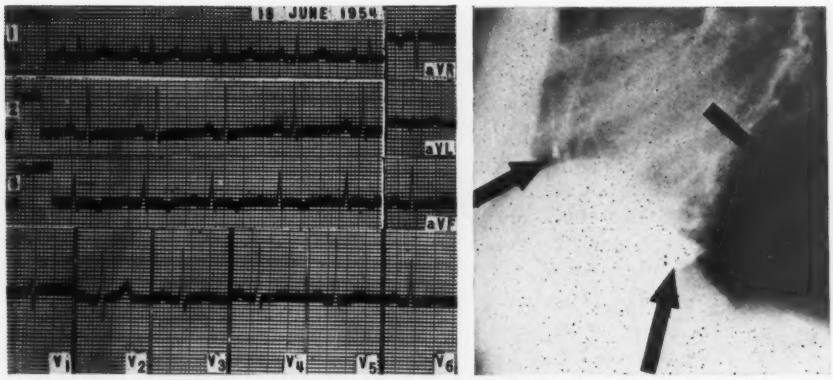

FIG. 7. Case 4. There is a broad P wave in lead II of the electrocardiogram. The T waves are flat in lead II and inverted in lead III. The T waves in lead V_4, V_5 and V_6 tend to be low. Calcification of the pericardium is evident in the lateral film of the heart.

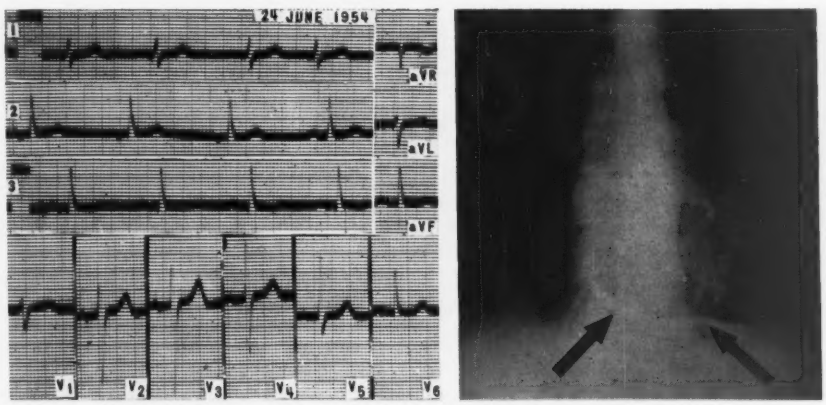

FIG. 8. Case 5. Apart from wandering of the pace-maker, the electrocardiogram is not remarkable. Diffuse pericardial calcification is present in the posteroanterior film of the heart.

wandering of the pace-maker. The x-ray film of the heart in the anterior view (fig. 8) shows a heavy band of calcification in the pericardium at the apex and over the right ventricle. Patchy calcification can be seen both posteriorly and anteriorly in the lateral film.

OBSERVATIONS

Calcification of the pericardium in five apparently healthy persons was demonstrated by x-ray examination in four instances and by autopsy in one. In three of the five cases calcification was not identified in routine chest films on at least one occasion. In each of these cases the electrocardiogram was grossly abnormal.

In the one case which came to autopsy, the coronary arteries were not significantly narrow and the myocardium was essentially normal except for superficial scarring.

In one case x-ray evidence indicated that the degree of calcification increased over a 12-year period.

The electrocardiograms varied widely, ranging from normal on the one hand to gross changes in form on the other. There were no major disturbances in rhythm and the P waves were normal in form with one exception. Auriculoventricular and intraventricular conduction were within normal limits. There were no changes in the form of the QRS complexes nor did any tracing exhibit low voltage, in fact voltage was of increased magnitude in one instance. The electrical position of the hearts varied from vertical to horizontal.

In three of the five records there was a definite depression of the RS-T segments. This occurred in lead II and in the left precordial leads in each instance but additional leads were involved in some records. Flat or inverted T waves in the limb leads and in a variable number of the precordial leads occurred in four of the five records. The RS-T segment depression and the T wave inversion occurred in the opposite direction to the main QRS deflection. Case 2 provided the only opportunity for a long term follow-up and here the observed abnormalities were constant.

Discussion

Notching of the P waves[3] and auricular fibrillation[1, 2, 10] are reported to be common occurrences in chronic pericarditis but neither was observed in the present series. Possibly such changes occur only when there is pronounced scarring over the auricles involving specifically the region of the sinoauricular node. This study suggests that these changes may be uncommon in asymptomatic persons.

The abnormalities of the ventricular complex characteristic of pericarditis are restricted to the RS-T segments and the T waves—the phase of repolarization. The view is commonly held[9, 10, 11, 12, 13, 14, 15, 16, 17] that these changes are the result of a disturbance in the subepicardial layer of the myocardium. During the acute inflammatory stage of pericarditis the RS-T segments are elevated and the T waves flat or inverted in one or more of the limb and precordial leads. With resolution, these changes tend to disappear. In chronic pericarditis the T waves are also flat or inverted but here the RS-T segments may be depressed. These changes occur in the opposite direction to the main QRS deflection. A residual adherent pericarditis with scarring of the outer surface of the myocardium may effectively delay the initiation of repolarization at this site, causing it to take place in a reverse direction, from the endocardium outward. If this is so it explains the observed changes and the fact that they tend to be irreversible.

RS-T segment depression has been recognized[9, 12, 19, 20] but not emphasized as part of the characteristic electrocardiographic picture of chronic pericarditis. Numerous examples of it are to be seen in the electrocardiograms of reported cases.[3, 11, 21, 22, 23]

Not infrequently reference is made to the occurrence of low voltage of the QRS complexes[2, 22, 24] in pericarditis. This reduction in voltage has been credited to the short circuiting effect of pericardial effusion[25, 26] or to the relatively poor conducting properties of thickened pericardial tissues,[22] and not to a decrease in the potentials of the underlying heart muscle which in many instances is singularly free from pathological change. In case 2 of the present series an increase in the QRS voltage occurred between 1945 and 1953. Here it is suggested that the heart, due to the contraction of adhesions between the pericardium and the anterior chest wall, was gradually tilted forward so that its anterior surface was brought progressively closer to the exploring electrode, resulting in voltages of increasing magnitude. The proximity of the anterior surface of the heart to the chest wall can be seen in the lateral film recorded Jan. 12, 1954 (fig. 5). It would appear that voltages of normal value as well as those which exceed these limits in either direction may be recorded in chronic pericarditis.

Subjects whose electrocardiograms show the RS-T segment and/or T wave changes which have been referred to should be subjected to a detailed x-ray search for calcification of the pericardium when these electrocardiographic alterations cannot be explained otherwise. It is to be understood, however, that failure to find calcification does not conclusively rule out the presence of pericardial scarring. The converse is equally true that a normal electrocardiogram may occur in the presence of recognizable pericardial calcification. Case 5 in the present series is an example and a similar case was reported by Forsee.[27]

Conclusions

The wide use of the "routine electrocardiogram" will include the examination of persons with pericardial scarring who have no symptoms of heart disease. Awareness by the cardiologist of the possibility of chronic pericardial scarring in persons so examined will make him particularly alert to tracings

showing normal QRS complexes with T-wave changes, particularly if the T waves point in a direction opposite to the main QRS deflection and are associated with RS-T segment depression. Low QRS voltage may or may not be present. The degree of suspicion will be increased if in serial records the abnormalities remain constant over a period of years.

Summario in Interlingua

Es presentate le casos de 5 apparentemente normal individuos con evidentia de calcification pericardial. Depositos de calcium se forma in le dense cicatrisation pericardial que es responsabile pro alterationes electrocardiographic. Le cardiologo qui es conscie del possibilitate de cicatrisation pericardial va esser specialmente alerte quando ille incontra electrocardiogrammas con normal complexos QRS e alterate undas T, particularmente si le undas T ha un direction opponite al principal deflexion QRS e es associate con un depression del segmentos RS-T. Un basse voltage QRS pote sed non debe esser presente. Le suspicion del cardiologo va augmentar se si registrationes serial revela que le anormalitates remane constante durante un periodo de plure annos.

Acknowledgments

The author is indebted to Drs. L. Hawirko, R. L. Howden and D. F. McIntyre, the Department of Transport and the Department of Veterans Affairs, Ottawa and the Great-West Life Assurance Company, Winnipeg for contributing to the clinical material used in this study.

It is a pleasure to acknowledge the painstaking photography of Sgt. J. E. Riley, R.C.A.F.

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Experiences with a New Oral Mercurial Diuretic—Merpurate

By Jerome G. Kaufman, M.D., Arthur Bernstein, M.D., Fred Weiss, M.D., Emanuel Klosk, M.D. and Harold S. Feldman, M.D., Ph.D.

A new oral mercurial diuretic, Merpurate, was studied in dogs for chronic toxicity and in humans for effectiveness. It was found that this product was effective as a diuretic in the doses used and gave a minimal number of undesirable reactions.

ORAL administration of diuretics with a safe and satisfactory diuresis has always been a therapeutic goal. Diuresis could then be accomplished at a slow but regular rate, with the avoidance of a sudden profuse diuresis,[1] which is very uncomfortable for the patient, and produces marked alteration of the fluid and electrolyte balance. Rapid diuresis has been known to cause attacks of gout,[2] tetany,[3] and cerebral thrombosis.[4] It has caused the low salt syndrome, and overdigitalization. Hence, slow diuresis is of some importance. Furthermore, oral diuretics avoid the necessity of frequent visits to the doctor and the financial burden thereof. They also eliminate the distasteful injections and allow the patient to handle his own care within safe limits.

The general recognition of the need of a safe and good oral diuretic without undesirable side effects is shown by the great number that have appeared upon the therapeutic scene in a relatively short span of time.

Pharmacology

Newer mercurial diuretics have been prepared from older agents by changing the mercury linkage in the molecule as well as by combining it with various members of the xanthine diuretics.

Merpurate,* chemically, is the hydrated crystalline double salt of calcium N-(β-methoxy - γ - mercuri - propyl) - 2 - pyridone-5-carboxylate and calcium theobromine. This new mercurial diuretic is a definite chemical entity containing 39.25 per cent theobromine, 4.3 per cent calcium, 9.8 per cent water and 45.58 per cent of N-(β-methoxy-mercuri-propyl)-2-pyridone-5-carboxylate. Elemental mercury content of Merpurate has been determined as 21.8 per cent based on the crystalline double salt.

Studies on Animals

Methods: Chronic toxicity studies were done on a series of mongrel dogs held in quarantine for 14 days at the Maltbie pharmacological laboratories. Merpurate dosage levels were assigned as 12 mg. per kilogram (two dogs), 20 mg. per kilogram (three dogs), and 40 mg. per kilogram (four dogs), with two dogs serving as controls. The drug was administered, orally, in capsules, twice weekly and an identical diet was fed to each animal.

Throughout the course of the study the weights of the animals were recorded twice weekly and renal function tests were performed prior to and following the administration of Merpurate. Routine laboratory examinations of the urine and blood of these animals were done after Merpurate was given to the experimental animals, for determining possible toxic effects.

Observations. Tables 1 through 4 describe the values of renal clearance and observations on the blood and urine obtained experimentally in the course of the six months' study. One can conclude from these data that Merpurate has little or no toxic effects on the kidneys or hematological picture.

No abnormal changes in growth or development occurred in any of the animals taking Merpurate for six months. After this period of time, the dogs were sacrificed and their organs were studied both grossly and microscopically,

From The Cardiac Clinic Of The Newark Beth Israel Hospital, Newark, N. J.

* Merpurate tablets supplied by Maltbie Laboratories Division, Wallace & Tiernan Incorporated, Newark 1, New Jersey.

TABLE 1.—*Values of Renal Clearance of Dogs Before Administration of Merpurate*

Dog No.	Wgt. Kg.	Date	GF (Creatinine)		RPF (PAH)		TMG (Glucose)	
			Per Dog	Per M²	Per Dog	Per M²	Per Dog	Per
15	12.5	4–2–53	43.6	72	155	256	180	298
2	8.5	4–1–53	42.6	91	162	348	125	268
3	10.5	4–14–53	47.3	88	133	248	150	278
5	7.5	3–31–53	36.6	85	139	324	199	465
1	11.0	3–30–53	48.0	87	169	304	154	278
12	11.5	3–27–53	51.0	90	143	252	192	336
14	11.1	3–26–53	63.9	114	173	310	110	198
7	7.7	3–25–53	38.7	89	139	318	94	214
9	11.3	3–24–53	38.3	82	127	273	161	346
13	10.0	3–23–53	41.0	79	167	322	88	169
11	10.2	4–17–53	35.9	68	143	272	38	72

for pathological changes. Specific aliquot portions of heart tissue, kidney, liver, spleen, brain, lung, and bone were analyzed for mercury content.

Cytonecrotic or degenerative changes that could be related to toxicity, were not observed in the organs studied. The only abnormal findings, bronchogenic abscess, isolated tubercles, interstitial pulmonitis, pulmonary fibrosis, interstitial nephritis, and mild pyelitis, were more probably the result of bacterial or virus infections or were mild reversible changes occurring in the course of such infections.

Table 5 lists the mean mercurial content of kidney, heart, and liver from the experimental animals, analyzed by colorimetric methods. The

TABLE 2.—*Values of Renal Clearance of Dogs before and after Administration of Merpurate*

Dog No.	Date	Before Merpurate After Merpurate	Dose mg/Kg	GF (Creatinine)		RPF (PAH)		TMG (Glucose)	
				Per Dog	Per M²	Per Dog	Per M²	Per Dog	Per M²
11	4–17–53	Control	0	35.9	68	143	272	38	72
	5–11–53			62	122	131	260	172	144
5	3–31–53	Before		36.6	85	139	324	199	465
	5–26–53	After 6 weeks	12	40.5	96	89	210	485	205
7	3–25–53	Before		38.7	89	139	318	94	214
	5–27–53	After 6 weeks	12	22	51	72	165	345	780
15	4–2–53	Before		43.6	72	155	256	180	298
	5–13–53	After 6 weeks	40	35.7	58	137	222	350	585
2	4–1–53	Before		42.6	91	162	348	125	268
	5–12–53	After 6 weeks	40	37.4	79.5	111	236	326	690
1	3–30–53	Before		48	87	169	304	154	278
	5–14–53	After 6 weeks	40	31	56	126	226	173	294
4		Before (not done)							
	5–15–53	After 6 weeks	40	33.6	70.5	97	201	212	443

TABLE 3.—*Blood Picture of Dogs Receiving Merpurate (Counts Made after 6 Months of Administration)*

Dog No.	Dose mg/Kg	Red Count (Millions)	White Count (Thousands)	Lym.	Neu.	Bas.	Eos.	Mon.	Hemoglobin (Sahli) Gm./100 cc.
1	40	6,220,000	7,400	23	63	2	7	5	16.0
2	40	5,850,000	7,500	34	58	1	0	8	15.0
4	40	5,530,000	9,600	52	43	1	0	4	15.5
15	40	6,010,000	10,800	39	56	0	3	2	17.0
9	20	7,060,000	11,200	39	50	1		8	18.0
12	20	5,100,100	11,200	44	48	0	2	6	13.5
14	20	6,610,000	8,800	37	56	2	5	0	18.0
5	12	6,580,000	10,700	27	58	0	11	4	16.5
13	12	6,040,000	7,400	18	72	1	5	4	15.5
8	Cont.	6,950,000	10,600	21	64	2	11	2	18.0
11	Cont.	5,660,000	9,000	30	66	0	2	2	14.0

TABLE 4.—*Dog Urinalysis*

Dog No.	8	11	12	13	1	2	4	5	14	9	15
Color	Straw	Straw	Straw	Straw	Straw	Straw	Amber	Straw	Amber	Straw	Amber
Appearance	Cldy.	Clear	Clear	Cldy.	Clear	Clear	Cldy.	Cldy.	Cldy.	Cldy.	Cldy.
pH	6.2	6.6	5.9	6.2	6.6	6.2	6.2	5.9	6.2	5.6	5.9
Sp-Gr	1.010	1.009	1.016	1.013	1.008	1.014	1.012	1.014	1.010	1.018	1.014
Albumin	Neg.	Neg.	Neg.	Neg.	Neg.	Neg.	Neg.	Neg.	1 Plus	Neg.	Neg.
Glucose (qual.)	Neg.	Neg.	Neg.	Neg.	Neg.	Neg.	Neg.	Neg.	Neg.	Neg.	Trace
Microscopic	Neg.	Neg.	Neg.	Neg.	Neg.	Neg.	Neg.	Neg.	Neg.	Neg.	Neg.

TABLE 5.—*Studies of Chronic Toxicity Produced by Merpurate. Mercury Analysis*

Hg Dosage	Hg Content					
	Kidney		Liver			
40 mg./Kg.	#1 0.110 mg	Mean 0.432 mg.	0.924 mg	Mean 1.089 mg.		
	#2 0.513 mg		1.200 mg			
	#4 0.615 mg		0.891 mg			
	#15 0.491 mg		1.300 mg			
20 mg./Kg.	#9 0.610 mg	Mean 0.527 mg.	0.997 mg	Mean 0.985 mg.		
	#12 0.402 mg		0.858 mg			
	#14 0.570 mg		1.100 mg			
12 mg./Kg.	#5 0.265 mg	Mean 0.255 mg.	0.630 mg	Mean 0.790 mg.		
	#13 0.245 mg		0.950 mg			
Control	#11 0.008 mg	Mean 0.007 mg.	0.015 mg	Mean 0.014 mg.		
	#8 0.005 mg		0.013 mg			
	Heart		Spleen	Brain	Lung	Bone
40 mg./Kg.	#1 0.015 mg	Mean 0.011 mg.	0	0	0	0
	#2 0.010 mg		0	0	0	0
	#4 .0 mg		0	0	0	0
	#15 0.020 mg		0	0	0	0
20 mg./Kg.	#9 .0 mg	Mean 0.009 mg.	0	0	0	0
	#12 0.018 mg		0	0	0	0
	#14 0.010 mg		0	0	0	0
12 mg./Kg.	#5 .0 mg	Mean .0 mg.	0	0	0	0
	#13 .0 mg		0	0	0	0
Control	#11 .0 mg	Mean .0 mg.	0	0	0	0
	#8 .0 mg		0	0	0	0

heart tissue of the animal receiving 20 mg. per kilogram was lowest for the mean range, yielding 0.009 mg. of mercury while the liver of the dog taking 40 mg. per kilogram was highest in the range, demonstrating 1.079 mg. The spleen, brain, lung, and bone samples of the dogs, revealed no mercury content at all.

Summary. It has been demonstrated in dogs that prolonged administration of Merpurate in dosage levels of 12 mg. per kilogram, 20 mg. per kilogram, and 40 mg. per kilogram produced no significant deviation from the normal (control animal), in regard to growth, kidney function, and hemopoiesis.

Gross and microscopic examinations of the dogs' vital organs demonstrated no cellular degeneration or necrosis.

STUDIES IN PATIENTS WITH CONGESTIVE HEART FAILURE

Method and Material. Our experiment was carried out with 26 patients who had been in congestive heart failure for at least six months prior to this test. They had all been digitalized, and were on a low salt diet. Each patient had been receiving at least one mercurial diuretic injection weekly in order to maintain cardiac compensation. All the patients in the study were ambulatory. Most of them were from the Cardiac Clinic of the Newark Beth Israel Hospital, but several were private patients.

Mercurial injections were stopped on all patients and the oral tablets was substituted. A low salt diet and digitalis therapy were maintained unchanged during the study. Depending on the condition of the patient, four types of administration were employed. When necessary the patient was switched from one dosage schedule to the other without the administration of injectable diuretics. The dosage schedules follow: (1) Sixteen tablets per week, i.e., one tablet after each meal and at bedtime on Monday, Tuesday, Thursday and Friday; (2) 32 tablets per week, i.e., two tablets after each meal and at bedtime on Monday, Tuesday, Thursday and Friday; (3) 28 tablets per week, i.e., one tablet after each meal and at bedtime, daily; and (4) 56 tablets per week, i.e., two tablets after each meal and at bedtime, daily.

The experiment was made on 26 patients, of whom 16 were male and 10 were female. Fifteen patients had arteriosclerotic heart disease, eight patients had hypertensive and arteriosclerotic cardiovascular disease, two patients had rheumatic heart disease, inactive, and one patient had syphilitic heart disease.

All patients were observed weekly by one of us. Blood pressures were determined and heart and lung auscultation was carefully checked. During each visit the weight was noted as was the level of peripheral edema and size of the liver. Fluoroscopic examinations of the lungs were made frequently.

All the patients were further studied at regular intervals by means of electrocardiograms, chest roentgenograms, determinations of blood urea nitrogen, and complete blood counts and urinalyses.

When feasible, the diuretic was discontinued and a placebo was substituted. This was done to make certain that we were treating patients who were still in congestive failure. The placebo looked exactly like the original diuretic tablet and the patient was not advised of the change. The placebo was continued until very definite signs of increasing failure were noted, i.e., increase in weight, basal rales, peripheral edema, etc. In all cases that developed failure, return to a dry state was attempted by the oral mercurial alone.

Results. Twenty-three of our 26 patients were maintained excellently without the addition of an injectable mercurial diuretic at any time. It was necessary at times to change from one plan of oral administration to another in order to control edema or failure. In all cases there was an excellent diuretic response to the oral tablets. Injectable mercurial diuretics were needed at crucial points in only three cases. Observations were carried out on some patients for as long as two years during this study. (See table 6.) There were no severe toxic reactions in any of the patients. Three patients showed a mild to moderate loss of appetite, which in all cases responded to a decrease in the daily number of tablets taken. One patient had bouts of vomiting. The evaluation was started while this patient was in uremia, the urea nitrogen being 90 mg. per 100 cc. of blood. He was kept on the drug for a total period of 20 months. Congestive failure was controlled during this entire period without difficulty and his renal status as well as his blood urea nitrogen remained unchanged.

Two patients developed diarrhea, but in neither case was it severe enough to necessitate stopping the drug.

One patient had some epigastric distress. This patient had an active duodenal ulcer. He was maintained on his ulcer routine without the necessity of stopping the oral mercurial. One patient with diabetes, on 40 units of neutral protamine Hagedorn insulin daily, had no change in his insulin or dietary requirements while on the oral mercurial tablet. One of the patients in this group found it impossible to take mercurial diuretic injections because of the severe leg cramps which he suffered thereafter. This patient was given a carbonic anhydrase inhibitor and immediately went into heart failure. She was then placed on Merpurate and has been maintained on the drug with complete comfort and compensation.

One patient, while being maintained on the oral drug, needed a prostatectomy. This was performed, and the patient was carried through the entire procedure without the addition of parenteral mercurial diuretics.

Ten patients were given a placebo and all mercurials discontinued. In all cases but one, the patients developed subjective and objective signs of increasing failure. All 9 patients who had developed failure were successfully returned to dry weight with the Merpurate tablets alone (fig. 1.).

Discussion

The search for an effective and safe oral mercurial diuretic is not new. Pioneer studies in this field were made by Batterman, DeGraff, and Rose in 1941.[5] Their work was followed by further studies with the same and other prod-

TABLE 6.—*Summary of Patients Studied*

Patient	Age	Sex	Diagnosis	Mercurial Inject. (no./wk.)		Length of Time on Exp.	Dosage of Oral Mercurial	Response	Toxic Reaction	Placebo	Reaction on Placebo	Notes
				Before Exp.	During Exp.							
1. I. N.	68	F	HCVD	1	0	20 wks.	28 tab/wk.	Good	None	12 wks.	Failure recurred	Present cond. good
2. P. G.	70	M	ASHD	2	0	9 mo.	56 tab/wk.	Good	Mild loss of appetite	Not used	—	Present cond. good
3. W. C.	58	M	HCVD	2	0	23 mo.	56 tab/wk.	Good	None	6 wks.	Failure recurred	Present cond. good
4. F. N.	73	F	ASHD	1	0	4 mo.	28 tab/wk.	Good	None	Not used	—	Did not return to clinic
5. J. S.	72	M	ASHD	2	0	4 mo.	56 tab/wk.	Good	Loss of appetite	Not used	—	Refused pills
6. S. R.	78	M	ASHD	2	0	14 mo.	28 tab/wk.	Good	None	Not used	—	Died; coronary occlusion
7. G. P.	72	M	SHD	1	0	17 mo.	32 tab/wk.	Good	None	9 wks.	Failure recurred	Deceased
8. S. E.	76	M	ASHD	2–3	0	20 mo.	56 tab/wk.	Good	Vomiting	6 wks.	Failure recurred	Died
9. L. H.	75	M	ASHD	2–3	0	15 mo.	56 tab/wk.	Good	Loss of appetite	Not used	—	Present cond. good
10. A. W.	75	F	ASHD	1	0	23 mo.	28 tab/wk.	Good	None	8 wks.	Failure recurred	Present cond. good
11. C. B.	58	F	HCVD	1	0	8 mo.	32 tab/wk.	Good	None	Pt. had no reaction on placebo		Released from exp.
12. C. S.	65	M	HCVD	3	1	15 mo.	56 tab/wk.	Good	None	Not used	—	Condition good
13. E. V.	89	F	ASHD	2	0	12 mo.	56 tab/wk.	Good	None	6 wks.	Failure recurred	Died; fractured hip; PM

14. S. Q.	70	F	ASHD	3	1	15 mo.	56 tab/wk.	Good	None	Not used	—	Diabetes; Cond. good
15. C. M.	70	M	ASHD	3	1	15 mo.	56 tab/wk.	Good	None	Not used	—	Response good
16. G. C.	58	M	HCVD	2	0	13 mo.	56 tab/wk.	Good	None	5 wks.	Failure recurred	Died; cerebral accident
17. D. O.	65	F	ASHD	2	0	15 mo.	56 tab/wk.	Good	None	5 wks.	Failure recurred	Rheumatoid arth.; response good
18. P. R.	41	F	RHD	2	0	9 mo.	56 tab/wk.	Good	None	Not used	—	
19. A. G.	58	M	ASHD	1	0	18 mo.	28 tab/wk.	Good	None	Not used	—	Response good
20. S. E.	78	M	ASHD	3	0	11 mo.	28 tab/wk.	Good	None	8 wks.	Failure recurred	Duodenal ulcer; became too weak to come to clin.
21. J. F.	52	M	RHD	1	0	5 mo.	32 tab/wk.	Good	None	—	—	Lost to clin.
22. J. A.	64	M	ASHD	1	0	12 mo.	32 tab/wk.	Good	None	—	—	Lost to clin.
23. F. M.	70	F	ASHD	1	0	6 mo.	28 tab/wk.	Good	None	—	—	Likes inject. better
24. M. K.	56	F	HCVD	1	0	8 mo.	16 tab/wk.	Good	None	—	—	Excellent response
25. A. A.	78	M	HCVD	1	0	12 mo.	28 tab/wk.	Good	None	—	—	On another mercurial oral; poor result
26. H. W.	79	M	HCVD	1	0	24 mo.	32 tab/wk.	Good	None	1 wk.	Failure recurred	Surgery done; continued good response to oral mercurial

ASHD—Arteriosclerotic Heart Disease.
SHD—Syphilitic Heart Disease.
RHD—Rheumatic Heart Disease.
HCVD—Hypertensive Cardiovascular Disease.

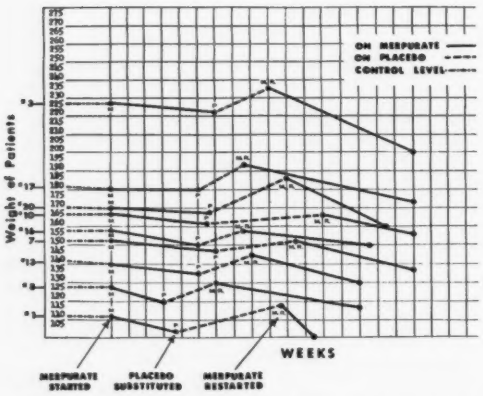

FIG. 1.—Weight Curves of Patients on Merpurate

ucts.[1, 6, 7] However, none was entirely satisfactory, since many side effects were produced when diuresis-producing doses were used. Therefore, the search for an effective oral mercurial diuretic has continued.

Recently several new and effective oral mercurial diuretics have come into use.[8-18] However, these too have had a fairly high incidence of side effects.[18] When we began our studies of Merpurate, we were somewhat disturbed to have for trial an oral mercurial diuretic which contained 20 mg. of mercury per tablet instead of the 10 mg. found in most other oral mercurial diuretics. We anticipated more side effects from the larger dose of mercury, even though the diuresis might be more effective. However, the combination of the mercury in the preparation used by us was apparently such that fewer unpleasant side reactions were produced than were seen with the other oral mercurial tablets. We did observe the need for larger doses with Merpurate to achieve a diuresis based on the larger mercury content, but nevertheless, the gastrointestinal disturbances were minimal.

With Merpurate, we found toxic manifestations had decreased tremendously over untoward results which we had encountered with other oral mercurial diuretics. Nausea, diarrhea, loss of appetite and vomiting, were present only to a very mild degree, and in no case was cessation of the drug necessary. Where any of the symptoms manifested themselves, a reduction in the dosage schedule was all that was necessary for its elimination.

We have found over a two-year period that Merpurate tablets were capable of replacing the parenteral drugs. In no case was it necessary to replace the oral tablet with parenteral therapy in the group studied. The effectiveness of this product was further established by the use of placebos in nine patients, in order to be certain that these patients still needed mercurials for control of their congestive failure. One of these patients had no diuresis with Diamox, a carbonic anhydrase inhibitor, but had excellent response when placed on the oral mercurial tablet, Merpurate, and was maintained free of failure.

No evidence of renal damage or of mercurial damage elsewhere was noted in any of these patients, in spite of the relatively large intake of mercury over a long period of time.

CONCLUSION

(1) A clinical study was carried out, using Merpurate, a new oral mercurial preparation, in patients, some of whom were maintained on the drug for as long as two years.

(2) Complete replacement of the parenteral drug could be accomplished.

(3) Dosage was an individual problem, but patients in chronic failure could be maintained on dosages ranging from 16 to 56 tablets per week (320 to 1120 mg. of mercury).

(4) There were no important toxic reactions noted. Electrocardiogram, chest x-ray findings, blood chemistry studies, urinalysis and blood count remained unaffected on the dosage of the drug used during the length of the experiment.

(5) From our study it appears that Merpurate is a safe and effective oral diuretic which can replace parenteral therapy in most patients.

CONCLUSION IN INTERLINGUA

1. Esseva executate un studio clinic con le nove diuretico mercurial, pro uso oral, que es fabricate sub le nomine Merpurato per le Division Laboratorios Maltbie del compania Wallace & Tiernan de Newark, New Jersey. Alicunes del patientes includite in le studio

esseva mantenite super Merpurato pro periodos de usque a 2 annos.

2. Il esseva possibile reimplaciar le droga parenteral completemente.

3. Le question del dosage esseva a regular individualmente, sed patientes in dysfunctionamento chronic esseva mantenibile con doses de inter 16 e 56 tablettas per septimana (320 a 1120 mg mercurio).

4. Nulle significative reactiones toxic esseva notate. Con le doses del droga usate per nos in le curso del integre experimento, il resultava nulle effecto significative super le electrocardiogramma, le radiogrammas, le studios hematochimic, le urinanalyse, e le contos sanguinee.

5. Ab nostre studio il appare que Merpurato es un efficace e non-riscose diuretico oral que pote esser usate con le majoritate del patientes como reimplaciamento del therapia parenteral.

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The Influence of Advanced Congestive Heart Failure on Pulsus Alternans

By JOSEPH M. RYAN, M.D., JAMES F. SCHIEVE, M.D., HUGH B. HULL, M.D. AND BERYL M. OSER, M.D.

Evidence is presented which indicates that in certain instances pulsus alternans may be abolished or diminished in the presence of advanced congestive heart failure. The observations suggest that in severe congestive failure the ventricular filling pressure may increase to the point where it causes the diastolic stretch of the left ventricle to be more equal from one beat to the next. This in turn would bring about more uniform systolic ejections and hence ventricular alternation would disappear or be lessened in degree.

PULSUS ALTERNANS is considered a grave sign of heart disease, indicating myocardial insufficiency.[1] Recent observations indicate that this phenomenon can be profoundly influenced by changes in the venous return to the heart. During the past two years we have encountered 12 patients with pulsus alternans and have noted that in certain instances advanced congestive failure may also influence pulsus alternans. We wish to report detailed studies of three of these patients.

MATERIAL AND METHODS

Three patients, all of whom showed pulsus alternans initially and who were on accepted treatment for cardiac failure were observed. One, who had rheumatic aortic insufficiency, was in heart failure following treated subacute bacterial endocarditis. Two observations were made on this man; the first, when he showed early signs and symptoms of left heart failure, and the second, when he was in intractable congestive failure seven months later. The remaining two patients had hypertensive heart disease with severe congestive failure as evidenced by dyspnea at rest, orthopnea, paroxysmal nocturnal dyspnea, venous distention, liver engorgement and peripheral edema. After the pulsus alternans was demonstrated, both were taken off all treatment for heart failure and were put on an unrestricted sodium diet for a period of 7 to 10 days. They were followed both symptomatically and by weight. Repeated observations were made of the arterial pulse. Treatment was reinstituted at the end of this period and again the pulse was recorded. All pulse curves shown were taken after the patient had been standing upright for a period of 20 to 30 minutes.

The direct arterial pulse was recorded simultaneously with the electrocardiogram and pneumogram, using string galvanometers. A Statham pressure transducer with a calibrated control box was used for the pulse curves.

RESULTS

Representative pulse curves of these three patients are seen in figures 1, 2 and 3.

Figure 1 shows C. B., a 29 year old white male, with rheumatic aortic insufficiency. When early heart failure was manifest, an alternans of 12 mm. was present. Seven months later when intractable congestive failure was present, the alternans had disappeared.

Figure 2 shows W. J., a 42 year old Negro man, with hypertensive heart disease. At the time of admission an alternans of 6 to 8 mm. was present. At that time he weighed 235 pounds. Off treatment for one week with a progression of symptoms and a weight gain of 5 pounds, the alternans had virtually disappeared. One week after treatment was restarted, the patient had improved symptomatically and had a weight loss of 28 pounds. Weighing 212 pounds, an alternans of 8 to 10 mm. was present. Two and one half months after treatment was restarted further improvement was noted. His weight was 185 pounds, and he was then edema free. An alternans of 16 to 18 mm. was seen.

Figure 3 shows A. R., a Negro woman, aged

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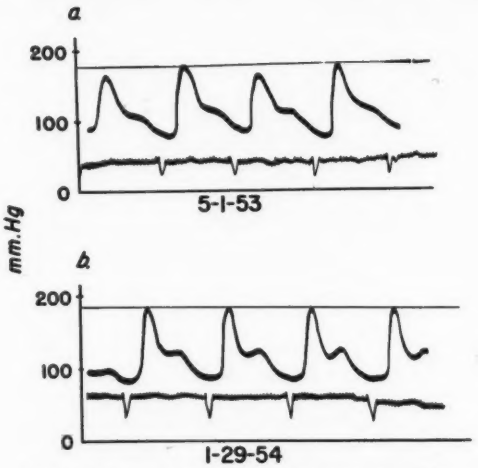

FIG. 1. C. B., a 29 year old white man with Rheumatic Heart Disease with Aortic Insufficiency. (*a*) At the time of early failure while on treatment; (*b*) At the time of severe intractable failure while on treatment.

This and the following curves are reproductions of the actual pulse tracings.

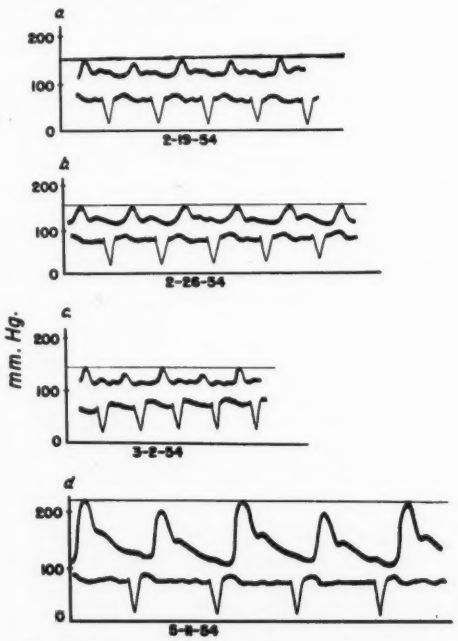

FIG. 2. W. J., a 42 year old Negro man with Hypertensive Heart Disease. (*a*) At the time of admission while on treatment; (*b*) One week after treatment discontinued; (*c*) Five days after treatment restarted; (*d*) Seven weeks after treatment restarted.

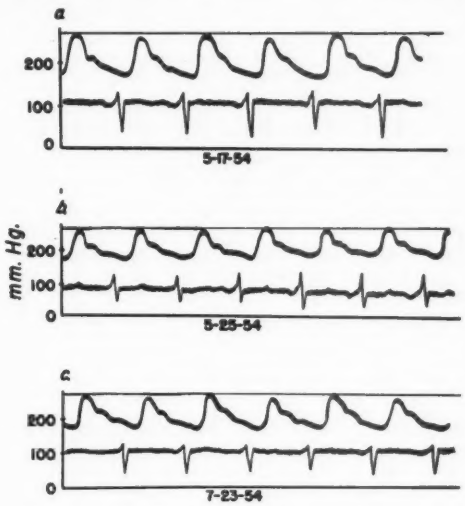

FIG. 3. A. R., 45 yr. old Negro woman with Hypertensive Heart Disease. (*a*) On admission while on treatment; (*b*) Nine days after treatment discontinued; (*c*) Two months after treatment restarted. Note the reduced sensitivity of curves (*b*) and (*c*).

45, with hypertensive heart disease. Two days after admission, the weight was 148 pounds, and an alternans of 10 mm. was noted. Ten days after treatment was discontinued, there was a weight gain of 4 pounds with progression of symptoms. Less than 5 mm. of alternation was demonstrable. Eight weeks after treatment was reinstituted the patient was improved. She then weighed 140 pounds although some edema was still present. An alternans of 14 mm. Hg was noted.

The results are summarized in table 1.

It might be pointed out that it has not been our experience thus far, for pulsus alternans to be exaggerated as congestive failure becomes more severe.

DISCUSSION

Our observations do not explain the actual cause of pulsus alternans but do seem to indicate that in some instances this finding may disappear or greatly diminish when heart failure becomes advanced. It would seem that, in the presence of severe congestive failure, the ventricular filling pressure may increase to a point where it causes the diastolic stretch of

TABLE 1. —

PATIENT	AGE	DIAGNOSIS	DATE	WEIGHT	SYMPTOMS	HEART RATE	mm Hg of ALTERNANS
C.B.	29	RHD	(a) ON R_1 5-1-53	125#	++	98	12m
		AI	(b) ON R_2 1-29-54	131#	++++	95	0
W.J.	42	HCVD	(a) ON R_1 2-19-54	235#	+++	120	6-8m
			(b) OFF R_2 2-26-54 1 week	240#	++++	115	0
			(c) ON R_2 3-1-54 5 days	212#	++	150	8-10m
			(d) ON R_2 5-11-54 7 weeks	185#	+	71	18m
A.R.	45	HCVD	(a) ON R_1 5-17-54	148#	+++	88	10m
			(b) OFF R_2 5-25-54 9 days	152#	++++	92	<5m
			(c) ON R_2 7-23-54 2 mo.	140#	++	98	14m

the left ventricle to be more equal from one cycle to the next. The ventricular responses would tend to become more uniform with more equal stroke outputs, and hence alternation would diminish. Support for this thesis is gained from the observations of Friedman and associates[2] and our own.[3] These latter studies showed that measures such as exercise, passive leg raising or infusions which increase the venous return to the heart lessen the degree of alternation. Conversely, any decrease in the venous return such as that caused by sudden tilting to the upright posture or venous tourniquets will exaggerate pulsus alternans.

We believe our findings do not conflict with previous observations that pulsus alternans may disappear or diminish with the addition of digitalis.[2, 4] Such cases do not, as a rule, appear to have a severe degree of heart failure and thus digitalis may improve myocardial efficiency to the extent that alternans diminishes or disappears when cardiac function approaches normal.

All of these observations suggest that, in some instances, there may be a certain range within which the ventricular filling pressure must lie, in order for ventricular alternation to occur. Should the pressure be brought below this range, as by digitalis, alternation would disappear. On the other hand if the pressure increased beyond this range, as in severe congestive failure, alternation would also disappear. We thus would have a situation where both improvement and deterioration in cardiac function can abolish pulsus alternans.

These studies in no way lessen the significance of pulsus alternans. We, like others, have not observed this phenomenon in the absence of organic heart disease. These observations do suggest, however, that the disappearance of pulsus alternans in severe congestive heart failure may be of clinical importance in that it may be another indication that failure is progressing. They further indicate that this phenomen might be more readily detected in certain patients after they respond to treatment for congestive failure.

SUMMARY

Three patients have been observed with pulsus alternans which virtually disappeared or greatly diminished with advanced congestive heart failure.

It is suggested that this finding may be brought about by a ventricular filling pressure which has increased to the point where it causes the diastolic stretch of the left ventricle to become more uniform from one beat to the next, thus bringing about more uniform systolic ejections.

SUMMARIO IN INTERLINGUA

Es presentate datos in supporto del conception que in certe casos pulso alternante pote esser abolite o reducite in le presentia de avan-

tiate dysfunctionamento cardiac congestive. Le observationes pare indicar que in casos sever de dysfunctionamento congestive, le pression de replenamento ventricular pote augmentar se usque al puncto ubi illo deveni capace a render le phase diastolic del ventriculo sinistre plus uniforme ab un pulso al altere. Isto, de su parte, causarea plus uniforme ejectiones systolic con le resultato que le alternation ventricular dispare o deveni minus marcate.

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The Relationship Between Impaired Retinal Vascular Reactivity and Renal Function in Patients with Degenerative Vascular Disease

By H. O. Sieker, M.D., J. B. Hickam, M.D. and J. F. Gibson, A.B.

In hypertension and diabetes retinal vascular changes which are evident on fundiscopic examination are usually accompanied by renal vascular changes which are evident on microscopic examination. It has been found that the retinal vessels of most patients with hypertension or diabetes fail to constrict normally when the blood oxygen tension is elevated. This investigation evaluates the clinical significance of decreased retinal vascular reactivity in patients with degenerative vascular disease by relating it to kidney function as measured by common clinical tests. The results of the study show that impairment of retinal arterial reactivity usually occurs in the course of degenerative vascular disease, particularly in hypertension, in advance of clinical evidence of altered kidney function. When clinical tests of renal function demonstrate renal damage, loss of retinal arterial and venous reactivity is marked.

IN HYPERTENSION and diabetes, pathological changes often occur in both retinal and renal vessels.[1-5] Retinal vascular changes which are advanced enough to be evident on fundiscopic examination are usually accompanied by renal vascular changes which are evident on microscopic examination.

Recently it has been found that the retinal vessels of most persons with hypertension and many with diabetes fail to constrict normally when the blood oxygen tension is raised.[6] This loss of vascular reactivity is thought to result from degenerative changes in the vessel wall and may be found in arteries and veins which show little or no change on ophthalmoscopic examination. When the vessels have become definitely abnormal in appearance, reactivity is almost always markedly diminished. Decreased reactivity to increased arterial oxygen tension, therefore, appears to be a sensitive index of degenerative changes in the retinal vessels.

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Dr. Sieker's work was done during tenure of a United States Public Health Service Postdoctorate Research Fellowship.

This investigation was supported by Contract AF 18(600)-554 monitored by the School of Aviation Medicine, Randolph Air Force Base, Texas, and by a grant from the Life Insurance Medical Research Fund.

Impairment of retinal vascular reactivity has been significantly correlated with a decrease in cerebral blood flow and cerebral vascular reactivity in arteriosclerotic patients.[7] The purpose of the present study was to investigate further the clinical significance of retinal vessel reactivity by relating it to the state of the kidneys, as determined by common clinical tests, in normal individuals and patients with degenerative vascular disease.

Methods

Observations were made in 97 hospital patients ranging in age from 12 to 76 years. This group includes 29 patients (the "control" group) without known renal disease, vascular disease or diabetes mellitus. The remaining patients had hypertension, diabetes, glomerulonephritis or pyelonephritis. The group did not include patients with congestive failure or prerenal azotemia which might cause transient changes in the tests by which the state of the kidney was evaluated.

Eyeground photographs were made under constant conditions with a Bausch and Lomb fundus camera while the patient breathed air and then tank oxygen. The visible diameter of the vessel was measured from the photograph with the aid of a low-power dissecting microscope containing a micrometric scale in the ocular. As described in a previous report,[6] retinal vascular reactivity was expressed as the per cent shrinkage in vessel diameter resulting from the patient's changing from air-breathing to oxygen-breathing. For ready translation into familiar clinical terms commonly used kidney tests were chosen. These were: urinary

TABLE 1.—*Retinal Vascular Reactivity in Hospital Patients Without Known Renal Disease, Vascular Disease, or Diabetes*

No. Subjects	Arterial Reactivity (%)		Venous Reactivity (%)	
	Mean	S.D.	Mean	S.D.
29	10.1	4.4	15.1	6.5

protein by the sulfosalicylic acid method, graded as 1 to 4 plus; phenolsulfonphthalein excretion and blood nonprotein nitrogen. The urine protein was estimated in all cases, the phenolsulfonphthalein excretion in 40 and the nonprotein nitrogen in 55.

The data for each test of renal function were analyzed separately. For a given test, the subjects were divided into groups according to the degree of abnormality shown by the test. The groups were then examined with reference to the retinal vascular reactivity to determine the extent to which changes in this function were correlated with changes in renal function. This procedure was followed for the total group of subjects. In addition, to provide a more homogenous group which would be expected to show changes in both retinal vascular reactivity and renal function the same procedure was followed for the hypertensive group alone. Hypertension was defined as a blood pressure which is usually in excess of 150 mm. Hg systolic and 100 mm. Hg diastolic. Statistical significance was taken to begin at the level $P = .05$.

RESULTS

The retinal vascular reactivity of the 29 "control" hospital patients without vascular disease is presented in table 1. These figures are in good accord with those previously found in normal subjects.[6]

The relationship between proteinuria and retinal vascular reactivity for all subjects is presented in table 2. In the group without proteinuria, the reactivity is slightly below the "control" value because some patients with vascular disease are included. The difference, however, is not statistically significant. With the appearance of proteinuria (trace to 1 plus), the arterial reactivity shows a large, statistically significant decrease. At this point, venous reactivity is not significantly altered from the group without proteinuria, but with the appearance of massive proteinuria (2 to 4 plus), venous reactivity also falls markedly.

When the comparison is made for hypertensive subjects (table 3), the arterial reactivity is significantly decreased below the control level just by virtue of the subjects being hypertensive even without proteinuria. As the proteinuria becomes massive, the arterial reactivity is further decreased. Venous reactivity, while not significantly decreased in the group without proteinuria, falls markedly with the appearance of protein in the urine. To view the picture in reverse, of the 18 hypertensive subjects who showed proteinuria only, two had

TABLE 2.—*Relation Between Proteinuria and Retinal Vascular Reactivity: All subjects*

Degree of Proteinuria	No. Subjects	Arterial Reactivity (%)		Venous Reactivity (%)	
		Mean	S.D.	Mean	S.D.
0	58	8.1	5.0	13.4	5.9
trace–4+	28	4.5*	5.2	10.7†	4.4
2–4+	11	1.6	2.9	4.4*	3.6

* Significantly less than the mean of the category just above.

† Significantly different from "control" group (table 1).

TABLE 3.—*Relation Between Proteinuria and Retinal Vascular Reactivity: Hypertensive Subjects*

Degree of Proteinuria	No. Subjects	Arterial Reactivity (%)		Venous Reactivity (%)	
		Mean	S.D.	Mean	S.D.
0	17	5.2*	4.9	12.9	3.9
trace–1+	11	4.4	5.5	8.5†	4.7
2–4+	7	0.6†	0.6	4.5	2.8

* Significantly less than "control" subjects without vascular or renal disease (table 1).

† Significantly less than the mean of the category just above.

TABLE 4.—*Relation Between PSP Excretion and Retinal Vascular Reactivity: Hypertensive Subjects*

2 Hour Total of PSP	No. Subjects	Average PSP Output/2 hrs.	Arterial Reactivity (%)		Venous Reactivity (%)	
			Mean	S.D.	Mean	S.D.
Above 60%	10	71 ± 7	4.4*	5.5	8.7*	4.5
Below 60%	15	38 ± 13	3.3*	5.0	8.4*	5.1

* Significantly different from control group (table 1).

TABLE 5.—*Relation Between Proteinuria, Phenolsulfonphthalein Excretion, and Retinal Vascular Reactivity*

Degree of Proteinuria	No. of Subjects	% PSP Excretion in 2 Hours	Arterial Reactivity (%)		Venous Reactivity (%)	
			Mean	S.D.	Mean	S.D.
0	14	62 ± 16	5.4*	5.0	11.9	5.9
trace–1+	17	55 ± 19	5.0	5.4	11.0*	4.4
2–4+	9	41 ± 26‡	1.7	3.3	5.0†	36

* Significantly less than "control" group (table 1).

† Significantly less than mean of category just above.

‡ Significantly less than PSP excretion of subjects with 0 proteinuria.

arterial reactivity within the normal range (8.1 and 19.5 per cent).

In general it appears that retinal arterial reactivity can easily be diminished without the appearance of proteinuria in hypertensive subjects. In all the subjects, the appearance of proteinuria indicates, to a high degree of probability, that retinal arterial reactivity is considerably reduced, and with massive proteinuria it tends to be further reduced. Venous reactivity follows the same general course, but the change is more gradual.

The test of phenolsulfonphthalein excretion was not done on subjects with a normal urine and nothing to suggest the possibility of renal disease. Consequently, the patients in whom it was performed constituted a specially selected group which proved to have a significant reduction below "control" values in both retinal arterial and venous reactivity. Several groupings of these subjects were made on the basis of different levels of phenolsulfonphthalein excretion, but no significant difference in arterial or venous reactivity of these groups was observed. The results for the hypertensive patients are presented in table 4. The subjects were divided into two groups; one with a normal two hour phenolsulfonphthalein excretion and the other with a reduced excretion. In both groups the retinal vascular reactivity was altered and it changed little as the phenolsulfonphthalein excretion declined. In the reverse view, of the 15 hypertensive subjects with a subnormal phenolsulfonphthalein excretion only two had arterial reactivity within the normal range (8.1 and 19.5 per cent). These were the same patients who had proteinuria and normal reactivity.

TABLE 6.—*Relation Between Serum Nonprotein Nitrogen and Retinal Vascular Reactivity: All Subjects*

Serum NPN (Mg. %)	No. of Subjects	Arterial Reactivity (%)		Venous Reactivity (%)	
		Mean	S.D.	Mean	S.D.
20–30	13	6.0[1]	4.8	14.5	6.4
30–40	27	4.8	4.8	9.8*†	2.9
Above 40	15	3.7	3.5	6.6*	5.2

* Significantly different from "control" group (table 1).

† Significantly less than mean in category just above.

TABLE 7.—*Relation Between Serum Nonprotein Nitrogen and Retinal Vascular Reactivity: Hypertensive Subjects*

Classification by Serum NPN	No. of Subjects	Average NPN (Mg. %)	Arterial Reactivity (%)		Venous Reactivity (%)	
			Mean	S.D.	Mean	S.D.
Below 40 mg%	17	33	3.6*	4.4	10.7*	4.5
Above 40 mg%	12	54	3.4*	5.5	7.4*	4.6

* Significantly different from "control" group (table 1).

In order to provide a better picture of the material on which this study was conducted, phenolsulfonphthalein excretion was compared with the level of proteinuria. The patients were divided according to the degree of proteinuria with the results presented in table 5. There is an apparent overall tendency for increasing proteinuria, decreasing phenolsulfonphthalein excretion and decreasing vascular reactivity to be associated.

As with the phenolsulfonphthalein excretion, the serum nonprotein nitrogen was determined in a selected group of patients whose overall picture indicated that it might be elevated. In consequence, the arterial reactivity of the group (table 6) is significantly below the "control" group even in the subgroup with a normal nonprotein nitrogen. In the first group venous reactivity is normal, but with the progressive increase in nonprotein nitrogen venous

reactivity shows a progressive and significant decline below normal values. When the analysis is confined to hypertensive subjects (table 7), retinal vascular reactivity is much reduced in the whole group with no significant difference between the groups with normal or elevated nonprotein nitrogen. Of the 12 patients with an elevated nonprotein nitrogen only two had normal retinal arterial reactivity. These were the same patients who also showed proteinuria and diminished phenolsulfonphthalein excretion with normal vascular reactivity.

Discussion

In a correlative investigation of this kind, interpretation of the results must, of course, be limited by the types of subjects used. This study included two general groups; one composed of hospital patients thought to be free of diseases which would affect the blood vessels or the kidneys and the other composed of patients with illnesses which are known to involve both systems. These were chronic illnesses, mostly hypertension, but included diabetes mellitus and chronic nephritis. In this group reactivity of the retinal arteries begins to be affected in advance of renal changes which produce marked proteinuria, diminished phenol sulfonphthalein excretion and increased nonprotein nitrogen. In the hypertensive patients severe impairment of retinal arterial reactivity occurred considerably in advance of evidence of renal damage. This functional evaluation is similar to the experience previously reported by Wendland on the basis of grading retinal and renal vascular disease by anatomical changes.[4] By the time evidences of renal damage are definitely established, retinal arterial reactivity is nearly uniformly decreased and retinal venous reactivity is impaired.

In the hypertensive group of 35 patients, only two had the combination of vascular reactivity within the normal range and impaired renal function. Previous pathological studies have shown that marked renal impairment without retinopathy suggests a renal basis for the vascular disease.[5] The clinical impression in these two patients was hypertensive cardiovascular disease and there was no evidence to suggest a primary renal basis for the hypertension. Four patients in the series were clinically diagnosed as having chronic renal disease, either glomerulonephritis or pyelonephritis; all had hypertension and all showed markedly impaired retinal vascular reactivity.

Account should be taken of the possibility that the retinal arteries of a hypertensive person might fail to constrict well in response to oxygen because they were already partially constricted or because constriction was opposed by the high intravascular pressure and not because of sclerotic changes in the wall. If the vessels were potentially motile but were already partly constricted, they should dilate relatively well in response to the proper stimulus. Retinal hypoxia will cause dilation of retinal arteries in both normal and hypertensive subjects, but the hypertensive vessels dilate less than the normal.[6, 8] The wall of the hypertensive artery shows less motility than the normal in either direction. Reduction of high intravascular pressures by the rice diet in a small group of hypertensives did not cause an immediate increase in arterial reactivity.[6] It is concluded that decreased retinal arterial reactivity in hypertensive subjects is not an artifact but depends upon pathological changes in the vessel wall.

This investigation, it is believed, has presented an objective method for assessing degenerative vascular changes, at least in the retinal vessels, and correlating that change with renal function in the living patient. The results emphasize that changes in the retinal arteries precede more overt evidence of impaired kidney function in degenerative vascular diseases, particularly hypertension. When overt signs of renal damage are manifest the retinal veins are also involved.

Conclusion

Impairment of retinal arterial reactivity usually occurs in the course of chronic degenerative vascular disease, and particularly in hypertension, in advance of clinical evidence of altered kidney function. When renal damage is apparent, loss of retinal arterial and venous reactivity is usually far advanced.

SUMMARIO IN INTERLINGUA

In hypertension e diabete il es un observation commun que le alterationes del vasos retinal, que es evidente sub le examine fundiscopic, es accompaniate per alterationes del vasos renal, que es evidente sub le examine microscopic. Il ha essite constatate que le vasos retinal del majoritate de patientes de hypertension o diabete non reage per un constriction normal al augmento del nivello oxygenic del sanguine. Le presente investigation provide un evalutation del signification clinic del reducite reactivitate del vasos retinal in patientes con morbo vascular degenerative per poner lo in relation con le function del renes, mesurate per methodos clinic usual. Le resultatos del studio indica que defectuositate del reactivitate del vasos retinal occurre usualmente in le curso del morbo vascular degenerative, specialmente in hypertension, ante omne signo clinic de alterate functiones renal. Quando essayos clinic del functiones renal demonstra un lesion renal, le perdita del reactivitate retinal arterial e venose es semper multo avantiate.

ACKNOWLEDGMENT

The authors gratefully acknowledge the technical assistance of Raymond Howard and Jane Kelly.

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The Hemodynamics of the Left Side of the Heart as Studied by Simultaneous Left Atrial, Left Ventricular, and Aortic Pressures; Particular Reference to Mitral Stenosis

By EUGENE BRAUNWALD, M.D., HOWARD L. MOSCOVITZ, M.D., SALOMAO S. AMRAM, M.D., RICHARD P. LASSER, M.D., SAMUEL O. SAPIN, M.D., AARON HIMMELSTEIN, M.D., MARK M. RAVITCH, M.D. AND ALVIN J. GORDON, M.D.

At operation the hemodynamics of the left side of the heart were studied in six patients without mitral stenosis, and in eight patients with mitral stenosis, by means of simultaneous needle puncture of the left atrium, left ventricle, and aorta. This technic permits analysis of the various phases of the cardiac cycle in normal subjects and in patients with mitral stenosis. The fundamental hemodynamic expression of mitral stenosis is the presence of an elevated left atrioventricular filling pressure gradient, which ranged from 4 to 20 mm.Hg, and after valvulotomy fell in relation to the adequacy of the procedure.

OUR knowledge of the human cardiac cycle has been retarded by the inability to study completely the hemodynamics of the left side of the heart. The technique of venous catheterization, which has contributed so much to an analysis of events in the right side of the heart of man[1-3] does not permit the direct study of the left heart chambers except in isolated instances of congenital communications between the right and left cavities.

Previous investigation of the left side of the circulation has been carried out primarily through animal experimentation. The classic studies of Wiggers[4-6] have defined the various phases of the cardiac cycle, as well as the pressure relationships between the left atrium, left ventricle, and aorta, both in the normal dog and in animals with experimentally produced valvular lesions.

Only sporadic investigations have been performed on the left side of the human heart. Limon and coworkers[7] recorded left atrial, left ventricular and aortic pressure by aortic catheterization. Left atrial pressures have been measured by needle puncture of the left atrium at the operating table,[8-10] through the bronchoscope,[11-13] through the chest wall,[14-16] and by cardiac catheterization in patients with interatrial septal defects.[17, 18] In addition, attempts have been made to estimate left atrial pressures indirectly by the so-called pulmonary capillary method.[19, 20]

Human left ventricular pressures have been obtained by needle puncture at operation,[21-23] by puncture of the chest wall,[24] and by catheterization of the left ventricle through a needle introduced into the left atrium through the chest wall[25] or through the left main bronchus.[26]

Pressures in the human aorta have been measured by retrograde arterial catheterization,[27-30] by puncture of the chest,[31] by needle puncture at the operating table,[32] and also by catheterization through a needle introduced into the left atrium through the chest wall.[33]

Simultaneous left atrial and left ventricular pressures in man have been measured by Wynn and associates,[8] by Bouchard and coworkers,[34] and by Venner and Holling.[35] Since these

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pressures were not recorded with manometers of equal sensitivity, they could not be employed directly for calculating time and pressure relationships. Venner and Holling have, however, superimposed and rescaled simultaneous left atrial and left ventricular pressure pulses in three cases of mitral stenosis and three cases of mitral insufficiency.[35]

We have recently described,[36] in preliminary form, a method by which simultaneous left atrial, left ventricular, and aortic pressures are obtained by needle puncture in the open chest, and are recorded with manometers of equal sensitivity with identical baselines. This report summarizes our experience with this technique in 14 patients.

Material

The patients studied were all on the ward and private services of The Mount Sinai Hospital.

Group I—Cardiovascular Normals

The three patients listed as cardiovascular normals consist of R. C., a 60-year-old white male with a tuberculoma of the left upper lobe; I. W., a 53-year-old white male who had an inoperable carcinoma of the left lower lobe, and O. W., a 16-year-old Negro girl with a mediastinal thymic cyst. None of these patients had any cardiovascular abnormality that could be elicited by a thorough history and physical examination, a 12-lead electrocardiogram, chest x-ray films and in one case (O. W.) by angiocardiography.

Group II—Other Patients Without Mitral Stenosis

This group consists of three patients. In two of these, studies were performed immediately after ligation of a patent ductus arteriosus. J. N. was 17 years old, while G. W. was 8. Both presented the classical clinical picture of uncomplicated patent ductus arteriosus. Both patients had normal electrocardiograms, and no cardiac enlargement by radiographic examination. Cardiac catheterization was performed on G. W., and normal pressures were found in the right side of the heart. The third patient in this group, A. B., was a 70-year-old male on whom the simultaneous pressures were obtained immediately after a left pneumonectomy for bronchogenic carcinoma had been performed. His past history, preoperative physical examination, electrocardiogram, and radiographic examination were all negative for cardiovascular disease. However, at the time of the study, the patient had a transient episode of nodal rhythm.

Group III—Patients with Mitral Stenosis

This group consists of eight patients with mitral stenosis who were studied several minutes before and after mitral valvulotomy. The pertinent findings related to these patients are summarized in table 1. All patients were considered on clinical grounds to have predominant mitral stenosis, and this was borne out by the findings at operation. One patient

Table 1.—*Cardiac Catheterization Data and Operative Findings in Patients with Mitral Stenosis (Group 3)*

Initials, Age and Sex	Functional and Therapeutic Classification	Cardiac Rhythm		Cardiac Catheterization Study (Pressures in mm. Hg)				Cardiac Index in L./min./M²	Arteriovenous O_2 Difference M/L.	Operative Findings	
				Right Ventricle systolic/end diast.	Pulmonary systol/diast.	Artery mean	"Pulmonary Capillary" mean			Valve Orifice Size Before Commissurotomy	Valve Orifice Size After Commissurotomy
E. H. 28 years, female	III C	NSR	Rest	68/8	70/35	48	27	1.8	59	finger	2–3
			10 min. ex.	—	103/56	76	—	—	—	tip	fingers
I. M. 34 years, female	II B	NSR	Rest	53/5	53/23	36	25	4.3	29	finger	1½–2
			10 min. ex.	—	74/33	50	—	—	48	tip	fingers
S. W. 45 years, male	III C	NSR	Rest	41/8	42/17	28	—	—	61	finger	1½
			10 min. ex.	—	73/28	45	—	—	79	tip	fingers
S. P. 37 years, female	III D	AF	Rest	69/5	73/32	50	—	2.6	52	finger	1½–2
			10 min. ex.	—	120/42	74	—	2.2	90	tip	fingers
E. S. 31 years, female	II C	AF	Rest	39/6	43/19	31	19	2.2	54	finger	3
			10 min. ex.	52/6	52/25	36	—	2.2	77	tip	fingers
F. S. 47 years, female	III C	AF	Rest	100/8	97/30	54	23	3.1	59	—	—
			10 min. ex.	142/9	147/80	104	—	2.7	73		
M. G. 42 years, female	II B	AF	Rest	31/6	28/10	19	16	3.1	49	1½	2–3
			10 min. ex.	—	45/20	31	—	2.9	82	fingers	fingers
S. K. 42 years, female	III C	AF	No Catheterization Performed							finger	2–2½
										tip	fingers

(S. W.) had a small degree of mitral regurgitation associated with mitral stenosis before valvulotomy, and this was increased as a result of the operation. Another patient (F. S.) had a shrunken atrium, almost entirely obliterated by thrombus material, not permitting access to the mitral valve. Accordingly, a mitral valvulotomy was not performed.

Method

The patients all had endotracheal intubation and were maintained under positive pressure respiration. The anesthetic agent was ether, occasionally supplemented by small amounts of cyclopropane. At the time the pressures were obtained, the left lung was partially collapsed, although it had been fully inflated for a short period immediately before.

The atrial needle was inserted through the auricular appendage, or through its stump after mitral valvulotomy. The ventricular needle was thrust perpendicularly through the lateral wall of the left ventricle, avoiding any small branches of the coronary vessels on the surface. The aorta was punctured at the level of the left subclavian artery in 11 patients, just above the aortic valve in two patients (I. M. and F. S.) and in the descending thoracic aorta in one (J. W.). The points of all three needles were estimated to be at almost identical levels.

Twenty-gage short-beveled needles were used. Specially made, thick-walled, vinyl plastic tubing with "luer-lok" adaptors was employed.* This tubing is 4 feet long, with an outside diameter of 0.262 inches and a bore of 0.073 inches. Three Statham P23A pressure transducers were mounted in tandem at identical levels. The zero point was the midatrial level as determined with the chest open.

A four-channel cathode ray photographic recording system was utilized, embodying three pressure channels and an electrocardiogram.† The paper speed was either 25 or 50 mm. per second, usually the latter. The characteristics of the recorder permitted direct superimposition of the three pressure tracings so that baselines and sensitivities could be made identical. Response of the system to pressure was linear to better than 1 per cent over the entire range.

Lead II of the electrocardiogram was recorded in all instances. Pressure measurements were averaged for a minimum of 15 beats in tracings with sinus rhythm, and for a minimum of 30 beats in tracings with atrial fibrillation. Mean pressures were determined by planimetric integration.

The pressure pulses obtained by the method described here do not reproduce the cardiodynamic events as faithfully as do those which have been obtained in animal experiments, with manometers thrust directly into the cardiac chambers.[6] On the other hand, our method probably interferes less with the action of the beating heart. Because of the obvious dangers to the patient, the problems of sterilization, and limitations of space in the operative field, it became necessary to utilize a system with a needle attached by a connecting tube to the pressure gauge. Such a system makes possible the recording of pressure pulses with less likelihood of artifacts than the technique of right heart catheterization in which catheter movement may impose considerable distortion.[37] However, some artifact produced by motion imparted to the needle and the connecting tubing by the beating heart has been unavoidable.

Other factors which have occasionally interfered with the accurate registration of the pressure pulse are the presence of thrombus material in the left atrium, and the damping effect of the apposition of the ventricular wall to the orifice of the needle.

It is apparent that general anesthesia, positive pressure respiration, and a partially collapsed lung will have influenced to a certain extent the pressure pulses obtained. Wiggers[4] has analyzed in dogs the changes in cardiodynamics, relatively minor, produced by the open chest. The most important of these are a prolongation of the isometric relaxation period, averaging .02 second, and greater variations in the relative duration of the maximum and reduced ejection phases.

Analysis of our curves indicates occasional minor inconsistencies. These may be attributed to difficulties in leveling the strain gauges, and slight inequalities in the levels of the three needle orifices. The divergence of the left ventricular and aortic pressure curves during ejection and protodiastole may be explained by the fact that the aortic needle was usually unavoidably introduced at some distance from the aortic valve. This could lead to a delay in the inscription of the aortic pressure pulse, as well as a minor modification of the contour occasioned by the transformation of the pulse wave as it traveled along the aorta.

Results and Analysis

Simultaneous needle puncture of the human left atrium, left ventricle and aorta appears to be both feasible and safe. We have now performed this procedure in 14 patients without any complication. In seven of these patients it was carried out both before and after mitral valvulotomy. No significant bleeding from any of the puncture sites has taken place and the only arrhythmia noted has been the regular occurrence of several ventricular premature contractions as the needle pierced the left ventricular wall. The experience of other ob-

* Manufactured by U. S. Catheter and Instrument Co., Glens Falls, N. Y.

† Manufactured by Electronics for Medicine, Inc., New York.

TABLE 2.—*Pressure Measurements (mm. Hg) in the Left Atrium, Left Ventricle, and Aorta of Patients Without Mitral Stenosis (Groups 1 and 2)*

Patient and Diagnosis	Left Atrial Mean	Left Atrial Mean Diastolic	Left Atrial "a" Wave	Left Atrial "c" Wave	Left Atrial "v" Wave	Left atrioventricular Filling Gradient	Left Ventricular Systolic	Left Ventricular Mean Diastolic	Left Ventricular End Diastolic	Aortic Systolic	Aortic Diastolic	Aortic Mean
Group I												
R. C. cardiovascular normal	—	—	—	—	—	—	88	3	5	84	44	61
I. W. cardiovascular normal	8	9	12	12	14	0	121	8	14	128	83	91
O. W. cardiovascular normal	7	7	8	8	11	1	79	6	10	77	49	61
Group II												
J. N. after ligation patent ductus arteriosus	4	4	6	6	7	0	79	4	4	81	37	49
G. W. after ligation patent ductus arteriosus	10	10	—	—	—	0	83	10	12	83	61	70
A. B. after pneumonectomy (nodal rhythm)	8	6	17		9	0	91	6	8	94	57	73

TABLE 3.—*Pressure Measurements (mm. Hg) in the Left Atrium, Left Ventricle and Aorta of Patients with Mitral Stenosis (Group 3) Before and After Valvulotomy*

Patient	Left Atrial Mean	Left Atrial Mean Diastolic	Left Atrial "a" Wave	Left Atrial "c" Wave	Left Atrial "v" Wave	Left Atrioventricular Filling Gradient	Left Ventricular Systolic	Left Ventricular Mean Diastolic	Left Ventricular End Diastolic	Aortic Systolic	Aortic Diastolic	Aortic Mean
E. H.												
Before valvulotomy	29	28	28	34	36	19	76	9	8	76	53	63
After valvulotomy	9	7	10	11	11	3	84	4	7	85	53	68
I. M.												
Before valvulotomy	26	24	23	25	29	14	94	12	15	95	58	81
After valvulotomy	21	19	19	23	29	8	95	12	12	99	65	89
S. W.												
Before valvulotomy	24	23	23	28	32	20	84	3	2	85	51	65
After valvulotomy	26	19	19	26	37	14	92	5	9	96	61	77
E. S.												
Before valvulotomy	24	23	atrial fibrillation	27	27	11	85	12	10	83	58	70
After valvulotomy	20	16		23	23	0	108	16	15	108	71	87
S. K.												
Before valvulotomy	11	8	atrial fibrillation	12	12	4	65	4	4	65	44	54
After valvulotomy	11	7		13	12	1	86	6	4	86	52	65
M. G.												
Before valvulotomy	13	12	atrial fibrillation	17	17	5	91	7	9	—	—	—
After valvulotomy	7	6		—	—	0	92	6	8	92	52	68
S. P.												
Before valvulotomy	28	27	atrial fibrillation	34	35	17	91	10	9	87	60	72
After valvulotomy	18	15		23	25	8	95	7	8	95	60	75
F. S.												
Before valvulotomy	29	28	atrial fibrillation	30	31	18	109	10	10	113	68	100

servers who have performed direct puncture of the heart chambers at the time of cardiac surgery confirms that this procedure is without danger.[8-10, 21-23, 32, 35, 36]

Detailed pressure measurements are presented in tables 2 and 3. Representative tracings are shown in figures 1 through 5.

Particular attention should be directed to the following pressure values: In the patients without mitral stenosis (groups I and II), the left atrial mean pressure ranged between 4 and 10 mm. Hg, the mean left ventricular diastolic pressure between 3 and 10 mm. Hg, and the mean left atrioventricular filling pressure gradient between 0 and 1 mm. Hg. In the patients with mitral stenosis (group III), the left atrial mean pressure measured between 11 and 29 mm. Hg, the mean left ventricular diastolic pressure between 3 and 12 mm. Hg, while the mean left atrioventricular filling gradient ranged between 4 and 20 mm. Hg before valvulotomy. Following mitral valvulotomy this pressure gradient fell significantly in every instance to values between 0 and 14 mm. Hg.

The Normal Cardiac Cycle

The cardiac cycle of the left side of the normal heart is depicted in figure 1. The definitions and symbols given to the various phases of the cardiac cycle by Wiggers[4] will be adhered to in this discussion.

Ventricular contraction begins at 1 and virtually simultaneously mitral valve closure occurs, as indicated by the crossover of the atrial and ventricular curves. The c wave in the left atrium begins at this time. This point marks the onset of the left ventricular isometric contraction period, which consists of a slow phase followed by a rapid phase of pressure rise. The isometric contraction period ends at 2, the moment of aortic valve opening, as indicated by the onset of the aortic pressure rise. The period of maximum ejection (2 to 3) lasts until the peak of the aortic pressure pulse (3) and is followed by the period of reduced ejection (3 to 4) which is completed at the beginning of the incisura (4), a point sometimes difficult to identify on our tracings. This marks the end of ejection and of systole. During protodiastole (4 to 5) the pressures in the ventricle and aorta continue to decline. This phase terminates at the moment of aortic valve closure (5), i.e., at the bottom of the incisura of the aortic pressure curve. Isometric relaxation (5 to 6) then follows and ventricular filling begins at the time the mitral valve reopens, which is indicated by the crossing of the atrial and ventricular pressure curves (6).

The period of rapid early filling, i.e., the diastolic inflow period, is marked by a continuous decline in the atrial pressure curve. Diastasis, or the period of slowed ventricular filling, begins when the atrial pressure begins to rise during diastole (7). The onset of the wave produced by atrial contraction marks the end of diastasis (8). The dynamic interval of atrial systole lasts until the peak of the atrial contraction wave (9), while the inflow phase which follows ends at the onset of ventricular isometric contraction (10) and completes the cardiac cycle.

The Cardiac Cycle in Mitral Stenosis

In patients with mitral stenosis the sequence of events differs in several important respects (fig. 2), and will of course vary somewhat when atrial fibrillation occurs. It has already been noted that in the presence of a normal mitral valve the crossing of the left atrial and left ventricular curves, the onset of the atrial c wave, and presumably the moment of mitral valve closure, all occur immediately after the onset of ventricular contraction. In contrast, in patients with mitral stenosis, since the left atrial pressure at the end of diastole is often significantly higher than the left ventricular pressure, the crossing of the left atrial and left ventricular curves and the onset of the atrial c wave are delayed until the left ventricular pressure rises to that of the left atrial. It is apparent, therefore, that the left ventricular isometric contraction period in mitral stenosis consists of two distinct phases. The initial phase, which actually may not be truly isometric, begins with ventricular contraction and lasts until the crossover of the left atrial

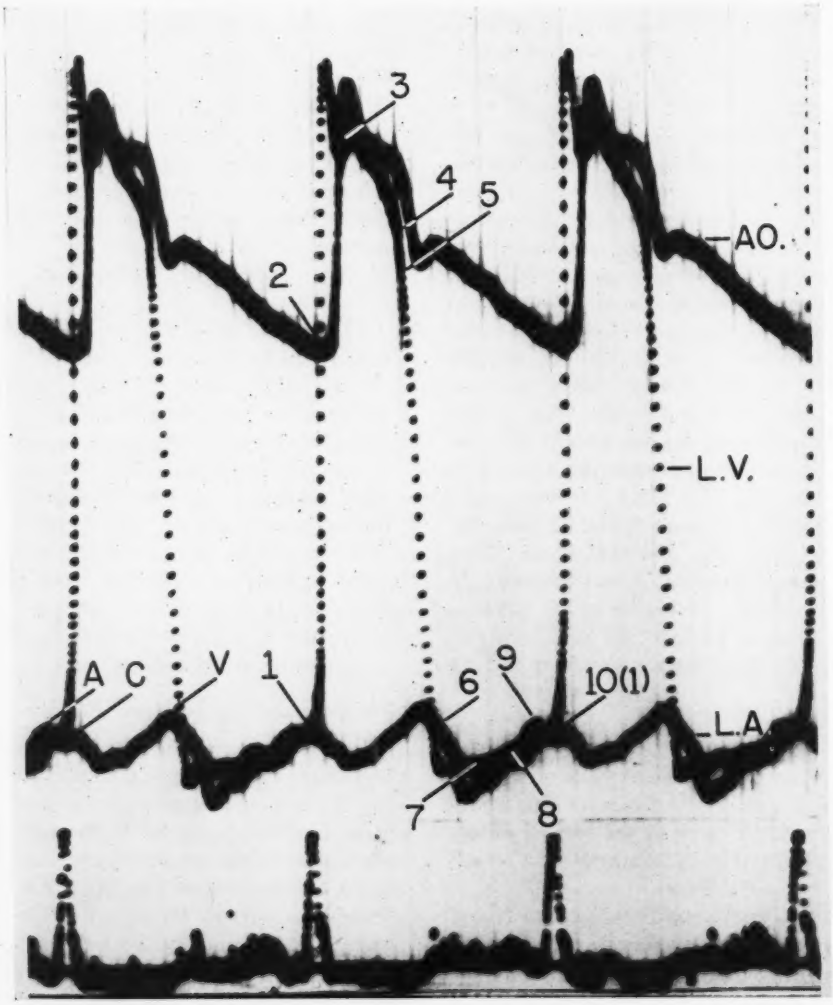

FIG. 1. The cardiac cycle of the left side of the normal heart (patient O. W.). For explanation of symbols see text.

and left ventricular pressure curves (×). It has not yet been established that this moment, (×), of crossing of the left atrial and ventricular curves in mitral stenosis represents the moment of closure of the stenotic mitral valve since closure could be delayed by the rigidity of the cusps.

Because of the presence of a positive pressure gradient between the left atrium and left ventricle at the beginning of ventricular contraction it is possible that the paradox exists in which the ventricular chamber fills while its wall is contracting. If this hypothesis is correct, left ventricular filling in mitral stenosis is not strictly limited to diastole, and the term "diastolic filling period" should not be employed. The final phase of isometric contraction begins with the crossing of the left atrial and left ventricular curves, and ends at the moment of aortic valve opening (2).

At the completion of isometric relaxation, that is, at the moment the mitral valve opens,

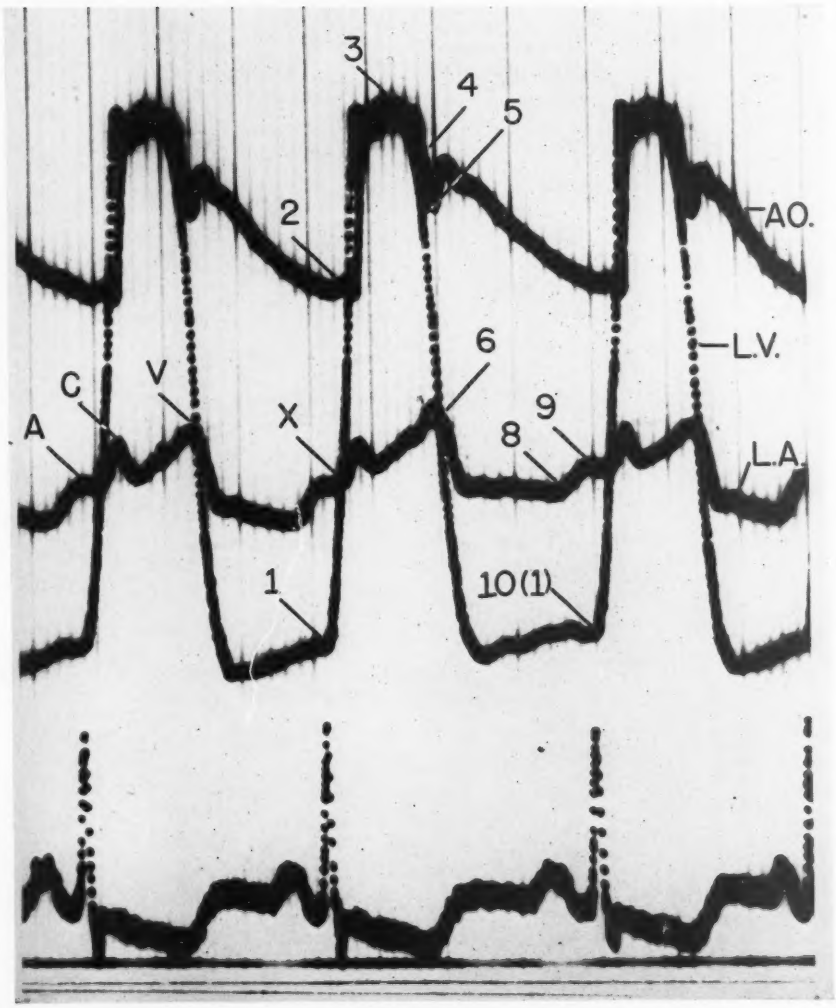

FIG. 2. The cardiac cycle of the left side of the heart in mitral stenosis (patient E. H.). For explanation of symbols see text.

there emerge other points of difference between the normal heart and that with mitral stenosis. Thereafter, in the normal, the left atrial and left ventricular pressure curves virtually coincide. Despite the fact that no measurable gradient appears to be present from the examination of some of our curves, a very small gradient must exist during diastole in order for blood to flow across the normal mitral valvular orifice. In contrast, in mitral stenosis after the mitral valve opens, the left atrial and left ventricular pressures diverge; the left ventricular pressure continues to fall while the left atrial pressure remains elevated, producing a distinct and easily measurable pressure gradient. This pressure gradient between the left atrium and left ventricle is the fundamental hemodynamic expression of mitral stenosis. It results in a slight shortening of the isometric relaxation phase and permits an earlier onset of mitral valvular opening and, therefore, of ventricular filling. It is thus ap-

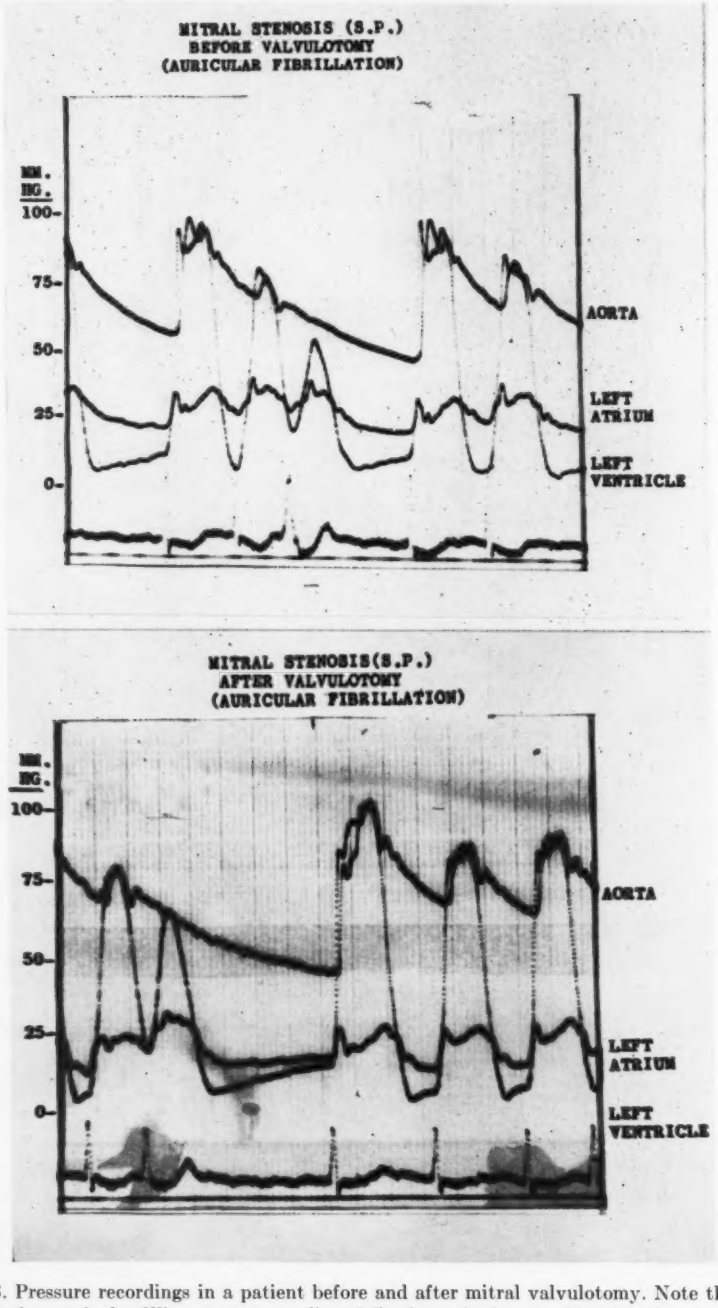

FIG. 3. Pressure recordings in a patient before and after mitral valvulotomy. Note the drop in the left atrioventricular filling pressure gradient following valvulotomy. The third beat in the upper tracing represents a "frustrate" ventricular contraction. The second beat in the lower tracing demonstrates that with prolongation of diastole the filling pressure gradient falls progressively.

parent that the time available for blood to flow into the left ventricle is increased by small increments at either end of the ventricular filling period.

A further difference between the normals and the patients with mitral stenosis whom we have studied is the absence of diastasis in the latter. The period of diastasis, as mentioned above, is that phase of diastole which is characterized by a rising atrial pressure before atrial contraction. Thus all of the left atrial pressure curves before valvulotomy were characterized by a continuous decline in pressure during diastole until atrial contraction.

Mitral Stenosis with Abnormal Rhythms

In patients with atrial fibrillation or other arrhythmias producing diastolic periods of varying durations, the magnitude of the left atrioventricular pressure gradient at the end of diastole varies inversely with the duration of the preceding diastole (figs. 3 & 4). A longer diastolic period presumably allows more effective emptying of the left atrium.

Among the other features of interest in the patients with arrhythmias are the following: the dynamics of "frustrate" ventricular contractions are well demonstrated in figure 3. The third beat in the upper tracing, a ventricular premature contraction deliberately induced by tapping the ventricle with a hemostat, does not raise the ventricular pressure to the level of the aortic pressure. Consequently, the aortic valves do not open, and the aortic pressure continues to fall uninterruptedly. The entire period between mitral valve closure and opening is, therefore, an isometric one. There is no ejection phase for the ventricular premature contraction, isometric relaxation following isometric contraction immediately. The presence in such a cycle of an atrial c wave, a finding we have confirmed in other cases, is further evidence that this wave is a function of ventricular contraction alone, and not related to the aortic pressure pulse.

In both A. B., a patient without mitral stenosis and, I. M., a patient with mitral stenosis, nodal beats were characterized in the atrial tracing by a greater pressure rise at the onset of ventricular contraction, presumably the result of summation of the a and c waves.

Changes Following Mitral Valvulotomy

Just as the presence of a filling pressure gradient between the left atrium and ventricle is the most significant finding in mitral stenosis, so does the abolition of this gradient constitute the chief object of mitral surgery.[38] However, changes in the filling pressure gradient brought about by valvulotomy must also be analyzed in the light of possible variation in the amount and character of the blood flow across the mitral valve. All other factors remaining unchanged, the left atrioventricular filling pressure gradient is dependent not only on the size of the mitral orifice, but also on the mitral valvular flow rate at the time the gradient is measured. If the mitral valvular flow rate increases, the pressure gradient required to force this additional volume of blood across the stenotic mitral orifice must likewise increase. The value of the knowledge of the alterations in the mitral valvular flow rate in evaluating the significance of changes in the left atrioventricular filling pressure gradient following mitral valvulotomy is, therefore, apparent. It is possible to estimate the direc-

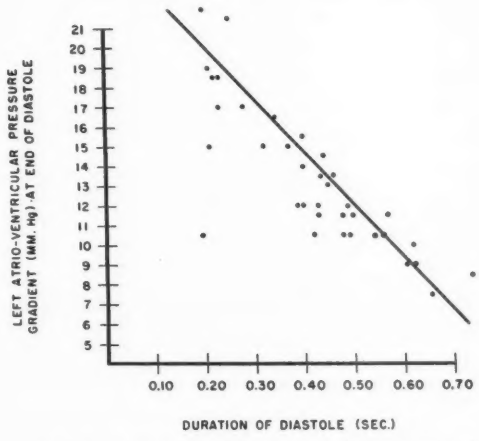

FIG. 4. The relation between the left atrioventricular filling pressure gradient at the end of diastole and the duration of the preceding diastole in patient S. P.

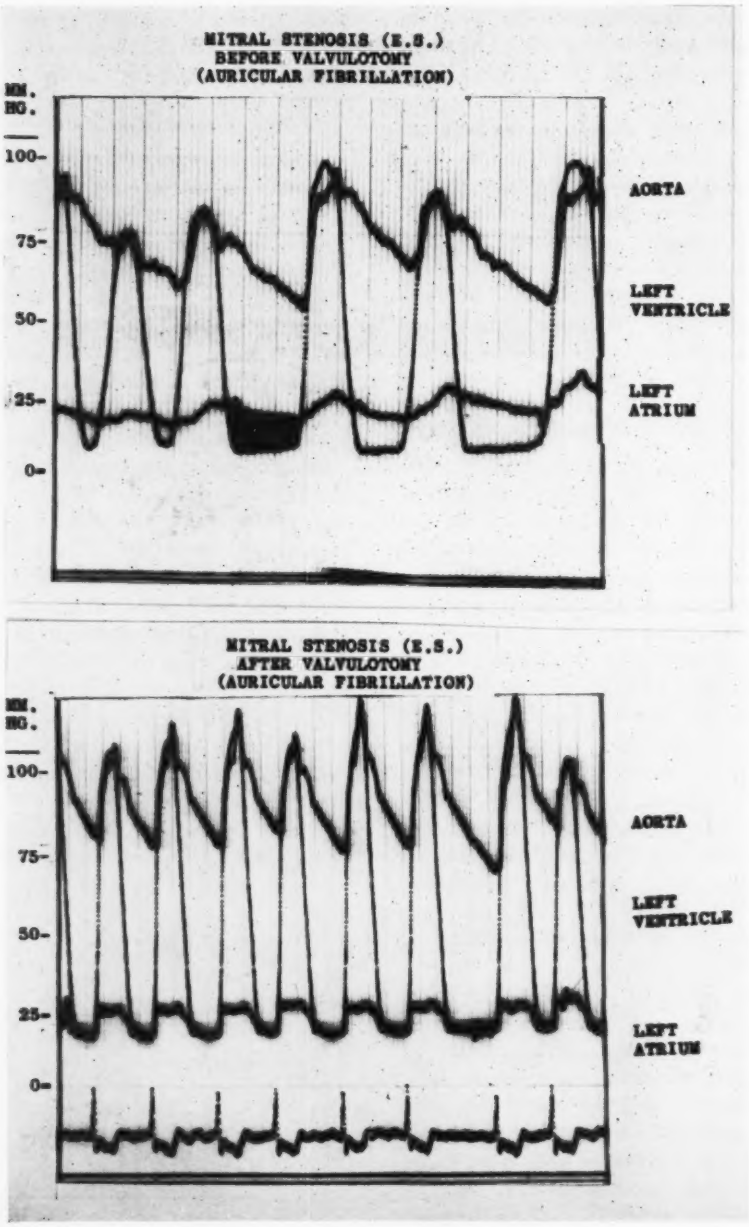

FIG. 5. Pressure recordings in a patient before and after mitral valvulotomy. Note that the elevated left atrioventricular filling pressure gradient (shaded in black in the third beat of the upper figure) has been completely abolished following the procedure in spite of the fact that the left atrial pressure remained elevated. Paper speed is 50 mm. per second in the upper, 25 mm. per second in the lower tracing.

tion and degree of change in cardiac output by applying Swan and associates'[39] modification of the pressure pulse method to the aortic pulses obtained from our patients before and after valvulotomy. We are unwilling to draw any final conclusions from such calculations until the validity of the method has been firmly established for mitral commissurotomy with its numerous and profound hemodynamic alterations.

Flow across a narrowed orifice, such as a stenotic mitral valve, is believed to be turbulent. The pressure gradient would then be expected to be directly proportional to the square of the flow, and relatively small changes in flow could produce significant alterations in the left atrioventricular filling pressure gradient. It is possible, however, that following surgical correction of the stenotic mitral valve the turbulent flow may be converted to laminar flow, and the pressure gradient would then vary with flow in a simple linear fashion.

If the postvalvulotomy left atrioventricular filling gradient is 0 or very close to 0 (as in patients S. K., E. S. (fig. 5) and M. G.), then the obstruction to blood flow offered by the mitral valve cannot be significant, no matter what the mitral valve flow or the heart rate may be. If there is a significant fall in the gradient, but this does not fall to or close to 0 and there is no fall in cardiac output or in heart rate, this fall in gradient may be related to the relief of the mitral stenosis.

It is apparent that the left atrioventricular filling gradient is a function of both the left atrial and left ventricular diastolic pressures. Following mitral valvulotomy, significant elevations in the left ventricular diastolic pressures were noted in several of the patients. This may represent a temporary effect on the left ventricle before it has adjusted itself to the altered dynamics produced by valvulotomy. In any event, it is apparent that the magnitude of the left atrial pressure does not clearly reflect the magnitude of the left atrioventricular pressure gradient, and that changes in the left atrial pressure following commissurotomy do not necessarily indicate identical changes in the left atrioventricular filling pressure gradient. For example, in E. S. (fig. 5), the left atrial mean pressure fell from 24 to 20 mm. Hg after valvulotomy, while the corresponding left atrial mean diastolic pressure fell from 23 to 16 mm. Hg. Since the left ventricular mean diastolic pressure rose from 12 to 16 mm. Hg, the left atrioventricular filling pressure gradient fell from 11 to 0 mm. Hg. Had the left atrial pressure alone been obtained, one could not have determined that the pressure gradient had been completely abolished by valvulotomy since the postvalvulotomy mean left atrial pressure of 20 mm. Hg and left atrial mean diastolic pressure of 16 mm. Hg are still elevated.

Summary

The hemodynamic events of the left side of the heart have been studied in detail in 14 patients. Needles were introduced into the left atrium, left ventricle, and aorta through the open chest, and the pressures recorded simultaneously on identical baselines at identical sensitivities.

In the six patients without mitral stenosis, the left ventricular mean diastolic pressure ranged between 3 and 10 mm. Hg. The mean left atrioventricular filling pressure gradient in these patients measured between 0 and 1 mm. Hg.

The elevated left atrioventricular filling pressure gradient is the fundamental hemodynamic expression of mitral stenosis, and its abolition constitutes the chief object of mitral surgery. In the eight patients with mitral stenosis this gradient ranged from 4 to 20 mm. Hg and following valvulotomy fell significantly in every instance, being almost entirely abolished in three patients.

The technique employed in these studies appears to be safe and makes possible the registration of three simultaneous pressure pulses with relatively little distortion.

Summario in Interlingua

Le hemodynamica del corde sinistre esseva studiate in detalio in 14 patientes subjicite a interventiones chirurgic. Quando le thorace habeva essite aperite, agulias esseva introducite a in le atrio sinistre, a in le ventriculo, e a in le aorta, e le pressiones in iste tres locos esseva

registrate simultaneemente per medio de manometros del mesme grado de sensibilitate con identic lineas de base.

Le gruppo studiate includeva 6 patientes qui non suffreva de stenosis mitral. In illes le valores median del pression diastolic sinistro-ventricular variava inter 3 e 10 mm Hg; le valores median del gradiente atrio-ventricular sinistre de pression replenatori mesurava inter 0 e 1 mm Hg.

Un elevate gradiente atrio-ventricular sinistre de pression replenatori es le expression hemodynamic fundamental de stenosis mitral. Su abolition es le objectivo principal del chirurgia mitral. In le 8 patientes con stenosis mitral, iste gradiente variava inter 4 e 20 mm Hg. Post valvulotomia illo se abassava significativemente in omne casos; in 3 casos illo esseva quasi integremente abolite.

Le technica usate in iste studios pare non-riscose. Illo rende possibile le registration simultanee de tres pressiones con un distortion que es relativemente negligibile.

ACKNOWLEDGMENT

The authors gratefully acknowledge the aid of Dr. Arthur Grishman in various phases of this study and of Dr. Robert Nabatoff who performed several of the mitral valvulotomies.

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Acute Complete Heart Block in Dogs

By T. E. Starzl, M.D., Ph.D., R. A. Gaertner, M.D. and R. Robinson Baker, M.D.

A study has been conducted immediately and up to 18 days after the surgical production of complete heart block in dogs. Immediately after surgery cardiac output, coronary flow, and mean arterial pressure were reduced in rough proportion to the degree of bradycardia. In time, these measures began to return toward preoperative levels. Paralleling the diminished left ventricular work was a diminished left ventricular oxygen consumption with little consequent change in myocardial efficiency. Small rises were detected in central venous pressure. At autopsy, the only unequivocal abnormality was myocardial hypertrophy which became measurable between 2 and 18 days after operation.

ALTHOUGH the clinical entity of complete heart block has been recognized for almost 100 years, few studies of the cardiocirculatory alterations in this condition are available, either in man or experimental animals. Human investigations have been limited to case reports or small series with differing results in terms of cardiac output, exercise adaptation and circulation time.[1, 2] Complete heart block in dogs, produced by crushing the auriculoventricular junction with a special clamp, was the subject of studies by Erlanger and his associates 50 years ago,[3-6] but this pioneer work was oriented primarily toward an understanding of the conduction mechanism. Eyster and Swarthout,[7] in 1920, produced complete heart block in dogs, by heating the region of the bundle of His and measured cardiac output and mean arterial pressure.

In addition to obtaining information which might have application to a human disease entity, experimental heart block furnishes a background to study the effect of extreme bradycardia upon cardiac function.

General Methods

Sixty mongrel dogs were used, ranging in weight from 12 to 25 Kg., and satisfactory technical conditions were realized in 46 experiments. The dogs were given 23 to 32 mg. per kilogram of Nembutal intravenously, and small implementing doses were used to keep a uniform anesthetic state. Tracheostomy was performed in acute experiments. When survival was contemplated, an orally placed endotracheal tube with an inflatable cuff was used.

Heart block was produced by section of the bundle of His through a right auricular myocardotomy during temporary occlusion of the cavae (8). In acute experiments, the conditions were imposed that the occlusion be no longer than 60 seconds (fig. 1) with less than 50 cc. blood loss, measured after collection in a suction bottle. All blood loss from surgical procedures or tests was replaced promptly with whole blood. In some animals repetitive cardiac stimulation was later performed by a technique described elsewhere[9] after reopening the thoracotomy.

Left ventricular coronary flow in cubic centimeters per 100 Gm. myocardium per minute was measured by the nitrous oxide desaturation method[10] after catheterization of the coronary sinus, pulmonary artery, and femoral artery. In these animals, cardiac output was determined by the direct Fick method. A closed system spirometer was used to measure total oxygen consumption. The blood samples were analyzed for nitrous oxide by the method of Kety and Schmidt,[11] and for oxygen content by the manometric method of Van Slyke and Neill. Efficiency and other calculations were computed by the formulae summarized by Goodale and Hackel[10] after weighing the left ventricle by their method. For these computations the myocardial respiratory quotient was assumed to be 0.83. In experiments in which coronary flow was not studied, cardiac output was obtained by the dye dilution method of Stewart and Hamilton, employing a repeatedly calibrated photometer which continuously measured the dye concentration of flowing arterial blood.[12]

Vascular pressures were detected with inductance or capacitance type transducers, with electrical integration of the mean pressures when desired. The frequency response curve of the measuring and recording systems was flat out to 30 cycles per second when measured by recording pressures

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Aided by a grant from the United States Public Health Service, H-226, National Institutes of Health, Bethesda, Md.

Presented at the fall meetings, American Physiology Society, Madison, Wis., September 1954.

within a balloon during explosion. Standard limb electrocardiogram, blue dye curves (T-1824), and vascular pressures were recorded on a four-channel direct writing oscillograph.

Results

Immediate Effects of Heart Block. Normal dogs under Nembutal anesthesia have tachycardia (in the present series the range was 125–240 per minute), and moderate hypertension.[13] During occlusion of the venae cavae and right auriculotomy, the arterial pressure dropped sharply to 15 to 40 mm. Hg. Small pulses continued to appear (fig. 1A) in the arterial tracing. It was apparent, also, from the varying amounts of blood which drained from the coronary sinus ostium into the operative field, that a reduced systemic flow continued. The reduced arterial pressure and coronary flow were evidently chiefly sustained by drainage from the pulmonary vascular bed to the left heart, a factor suggested by the extreme blanching of the lungs during the period of caval occlusion. During this time the peripheral venous pressure rose to 250 to 400 mm. saline.

After closure of the auricle and release of the cavae, strong arterial pulses immediately reappeared (fig. 1A) with idioventricular rates of 25 to 67 per minute. There was, in general, a transient period of hypertension. Within a minute the arterial pressure became stabile (A) with systolic pressures at about the same level as were present before the block, lower diastolic pressures than before, and consequent lower mean blood pressures (fig. 1A). Venous pressures likewise promptly returned toward control status, but generally retained an elevation of a few millimeters of saline.

Electrocardiographic confirmation of the block was obtained (fig. 1B). However, presence of block was evident at the operating table, even while the auricle was still open, because of the gross auriculoventricular dissociation and extreme ventricular slowing. In no case did a ventricular rhythm fail to start after the block.

The resulting preparation was a very stabile one. In four animals the rate, cardiac output, and arterial and venous pressures were followed from 15 to 150 minutes during which time little significant change occurred in any of these

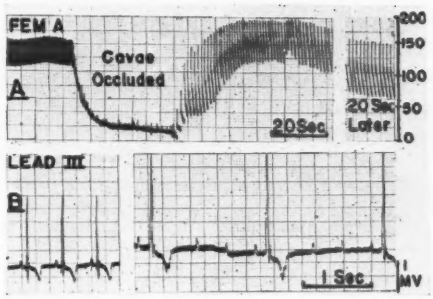

FIG. 1. A. Femoral arterial pressure before, during and after caval occlusion and section of the bundle of His. Calibration in mm. Hg. B. Electrocardiogram of sinus and idioventricular rhythm before and 15 minutes after surgically induced complete heart block. Different animal than A.

measures. Because of the tendency to maintain a *status quo*, data in subsequent experiments was usually obtained only at one to one and one half hours after the block.

The Effect of Acute Heart Block on Cardiac Output. Cardiac output, using either the Fick or blue-dye method, was determined in 30 dogs before and 60 to 90 minutes after complete heart block. After the operative procedure, the chest was closed with water seal drainage, so the thoracotomy had generally been closed for at least 45 minutes before post-block determinations. In some cases the pre- and post-block studies were done while the animals were on a positive pressure respirator, supplied with 100 per cent oxygen, and the results followed the same pattern as when respirations were spontaneous and with room air.

In every one of the 30 experiments, the minute output of the heart was reduced, a general conclusion which was also reached by Eyster and Swarthout.[7] The magnitude of the decline was related to the idioventricular rates which ranged from 25 to 67 per minute (fig. 2). The greatest number of animals had rates of from 40 to 55 per minute, and in this group the cardiac output fell quite regularly to about one half of the value previously obtained with an intact conduction system. With idioventricular rates faster or slower than this, cardiac output was curtailed less or more severely, respectively (fig. 2). After several experiments, it became apparent that the

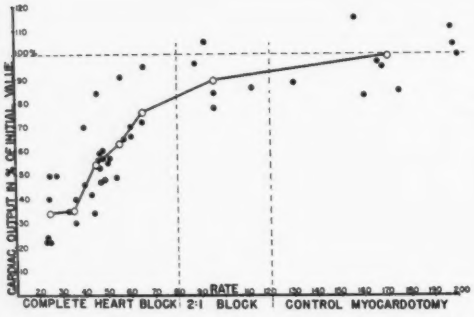

FIG. 2. Effect of complete heart block, 2:1 block, and control myocardotomy on cardiac output. Note how the magnitude of the cardiac-output fall is related to the degree of bradycardia. Values are expressed in per cent of preblock values, each animal serving as its own control.

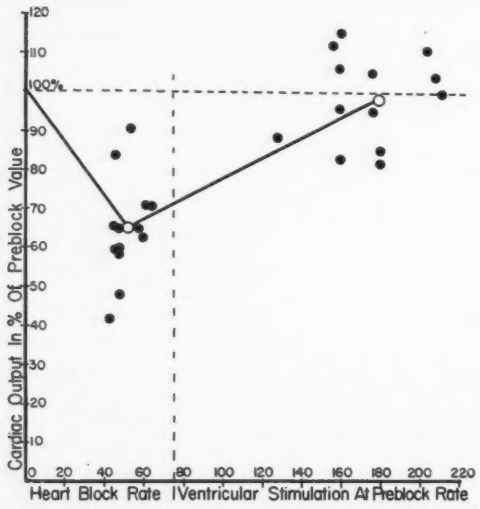

FIG. 3. Cardiac outputs, expressed in per cent of preblock values, in 13 dogs in which complete heart block was produced and ventricular stimulation then conducted at the same rate as had been present before the lesion. Note the fall in output after block, with subsequent restoration to preoperative values during ventricular pacemaking.

cardiac output with idioventricular rhythm could be roughly predicted, by the fraction $\frac{block\ rate}{90} \times control\ cardiac\ output.$

In five animals, 2:1 heart block was inadvertently produced, with rates of 85 to 112 per minute. In these animals, cardiac output was reduced an average of only 10 per cent (fig. 2). In nine other cases, the right auricle was opened during a 60-second caval occlusion in exactly the same manner as in performing a block, but without section of the bundle of His. In these controls the cardiac output was essentially unaffected (fig. 2).

The foregoing data is strong evidence that the decreases in minute output of the heart were due specifically to the extreme bradycardia resulting from section of the bundle of His. To further rule out the possibility of nonspecific effects due to the operative procedure, ventricular stimulation, at the rate of the preblock heart beat, was performed in 13 animals with complete heart block. Such repetitive stimulation restored the cardiac output to levels present before the block (fig. 3).

In order to follow any further alterations in cardiac output in the later postoperative period, seven dogs were studied 2 to 18 days after establishment of complete heart block. In this group, all pre- and postoperative determinations were done by the Fick method, in conjunction with coronary flows. The results are shown in figure 4, and for comparison, the data obtained acutely under identical test conditions is included. Three dogs were studied 48 hours after the heart block and then sacrificed. The cardiac output had returned on the average to 70 per cent of preoperative values, in contrast to a general 50 per cent reduction found acutely (fig. 4). This improvement coincided with larger stroke volumes. In four other dogs, similar studies were done 10 to 18 days postoperatively. In these animals the minute output of the heart averaged about 80 per cent of the preblock figures (fig. 4). Comparative stroke volumes had also increased.

To generalize, it has been shown that after heart block, the cardiac output is acutely reduced to an extent dependent upon the degree of rate slowing. Bradycardias as low as 90 beats per minute are attended by stroke-volume increases of such a magnitude that the cardiac output is not greatly affected. With idioventricular rates slower than this, further stroke volume increases evidently do not occur, and cardiac output is diminished as the fraction $\frac{idioventricular\ rate}{90}$. This state of reduced out-

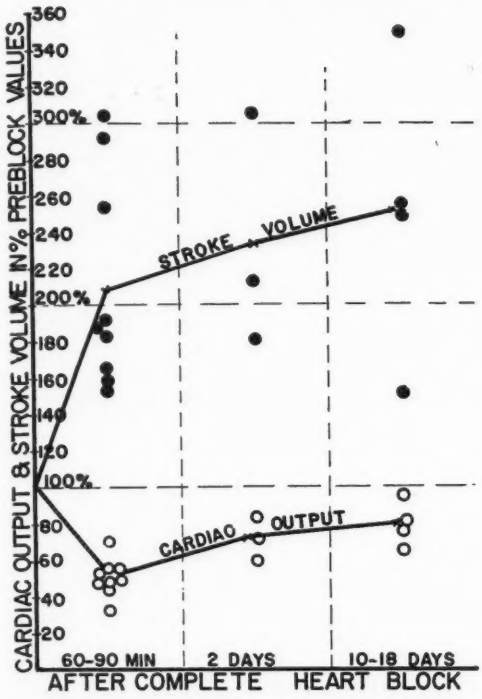

FIG. 4. Changes in cardiac output and stroke volume in animals studied one to one and one half hours, two days, and 10 to 18 days after surgically induced complete heart block. Results are in per cent of preoperative values, each animal serving as his own control.

put is quite stable for the first few hours. Within 48 hours, the cardiac output begins to return toward control values, subserved by increasing stroke volume. This compensation continued with time, but even after 10 to 18 days, the cardiac output was still only 80 per cent of preoperative values.

The Effect of Acute Complete Heart Block on Total Oxygen Consumption and Systemic Arterial-Venous Difference. As might be expected, the metabolic requirements of dogs with complete heart block were not greatly changed. The total oxygen consumption one to one and one half hours after the block was in most cases slightly reduced, averaging 90 per cent of the preblock uptake (fig. 5). In the dogs studied after 2 to 18 days, total oxygen consumption averaged 15 to 20 per cent greater than preoperatively. This elevation was probably a nonspecific effect such as is frequently noted clinically after major surgical procedures.

With the minimally altered oxygen consumption and reduced cardiac output, tissue oxygen needs were met by an increased extraction of oxygen from the blood (fig. 5). Acutely, the average arterial-venous difference was doubled. At 2 and 18 days, a progressive decline in the arteriovenous difference occurred coincident with the return toward normal of the cardiac output. In no animal, however, did the arterial-venous difference return completely to normal (fig. 5).

The Effect of Complete Heart Block on Arterial Pressure. A few minutes after complete block was established, systolic pressure usually stabilized at about the same level as had been present with the preoperative sinus rhythm (fig. 1), an observation which had been previously recorded by Erlanger.[3] The diastolic pressures with the slowed rate were considerably reduced with the development of large pulse

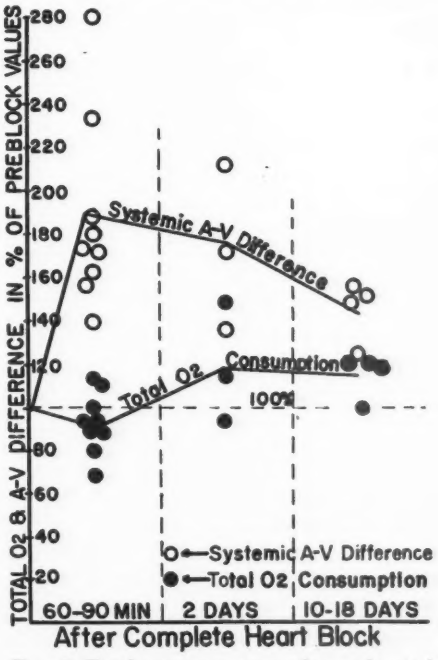

FIG. 5. Total oxygen consumption and arterial-venous difference at different times after surgically induced complete heart block. Results are in per cent of preoperative values, each animal serving as his own control.

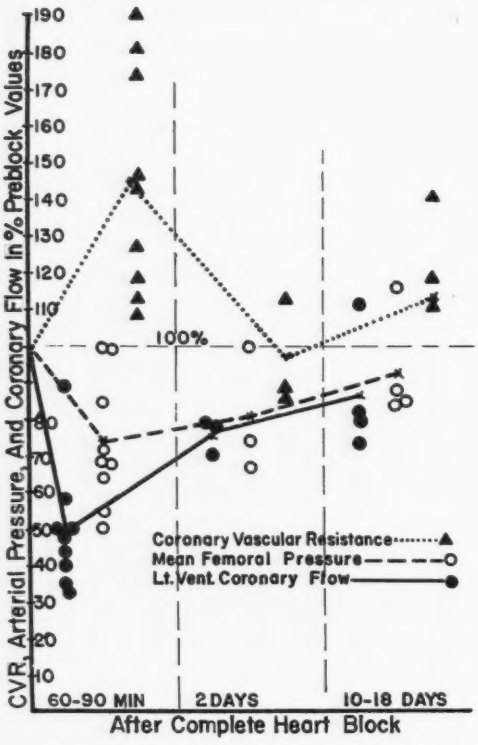

FIG. 6. Changes in left ventricular coronary flow, mean femoral pressure, and coronary vascular resistance (CVR) at varying times after surgically induced complete heart block. Results are in per cent of preoperative values, each animal serving as his own control.

pressures (fig. 1). Mean arterial pressures were consequently reduced (fig. 6) in agreement with earlier data of Eyster and Swarthout.[7] The decline in mean arterial pressure was roughly proportional to the degree of rate reduction. During the first 18 postoperative days, a gradual elevation of mean (fig. 6), diastolic, and systolic pressures occurred. In only two of the seven cases shown, however, did complete restoration of the mean pressure to preblock levels occur (fig. 6).

The Effect of Complete Heart Block on Left Ventricular Coronary Flow and Coronary Vascular Resistance. Sixty to 90 minutes after completion of the block, the coronary flow was reduced in all dogs studied, with an average decline of 50 per cent (fig. 6). The diminution in coronary flow was greatest in the animals with the slowest rates. In the animals studied at two days, coronary flow had returned to 75 per cent of preoperative values, and in 10 to 18 days a further return toward but not to preblock values had taken place (fig. 6). In the animals studied during the first one and one half hours after block, the arterial-coronary sinus extraction was in every case slightly reduced. The intact controls had an average extraction of 11.3 volumes per 100 cc. and the acutely blocked dogs had an average extraction of 9.2 volumes per 100 cc. This change was less pronounced in the animals observed from 2 to 18 days. In the latter group, average extraction in the preoperative controls was 10.8 volumes per 100 cc., and after block was 9.9 volumes per 100 cc.

Coronary vascular resistance was computed in arbitrary units from the formula

$$\frac{\textit{mean arterial pressure}}{\textit{coronary flow/sec./100Gm. left ventricular muscle}}$$

One to one and one half hours after the operative procedure, some degree of coronary vasoconstriction, relative to the preblock status, was evident in all the animals studied (fig. 6). In the 2 to 18 day group of animals, however, the coronary vascular resistance was not greatly altered in comparison to previously performed control studies on the same animal (fig. 6).

The Effect of Complete Heart Block on Left Ventricular Work, Oxygen Consumption, and Efficiency. Left ventricular work was computed from cardiac output times mean femoral pressure. The calculation ignores the work done in imparting velocity to blood, a factor which is ordinarily less than 2 per cent of total work. This kinetic factor may be increased with the pronounced bradycardia and large stroke volumes[14] seen with complete heart block. Although it is unlikely that the kinetic work becomes any greater than 10 per cent of the total ventricular work, it is possible that the work calculations were falsely low to this degree. It has been previously noted in this study that both mean femoral pressure and cardiac output were reduced. Work, the product of these determinations, was reduced in the manner

shown in figure 7. Acutely, left ventricular work was diminished to one third of the preblock value. With temporal passage, work returned toward control values. From 10 to 18 days after the heart block, the work had returned to an average of 80 per cent of preoperative figures (fig. 7).

Left ventricular oxygen consumption was calculated from the formula

coronary flow × *coronary oxygen extraction* × *left ventricular weight.*

As will be described subsequently the animals acquired varying degrees of myocardial hypertrophy after a few days. In all cases in which the animals were kept for 10 to 18 days, the preoperative weight, for use in the computation, was estimated by the method of Goodale and Hackel.[10] Postoperative calculations were based on the actual postmortem left ventricular weights. It is evident from a glance (fig. 7) that left ventricular oxygen consumption closely paralleled the work load of the left ventricle. Acutely, oxygen consumption sustained an abrupt fall, with a subsequent return toward preoperative levels.

Left ventricular myocardial efficiency was calculated from

$$\frac{\textit{actual work}}{\textit{work equivalent of oxygen used}}$$

Because of the well known tendency of the isolated heart to function more economically at slowed rates,[15, 16] it was anticipated that myocardial efficiency would be increased in animals with an idioventricular rhythm. This was not the case, although in chronically blocked dogs with complete return to preoperative work level, rises in efficiency have been noted.[8] With the close relation between work done and left ventricular oxygen utilization, the average efficiency was changed very little in the present series (fig. 7), either acutely or in 2 to 18 days. In actuality, a slight decline in efficiency was seen, possibly related to falsely low work values (see above).

The Effect of Complete Heart Block on Right Auricular Pressures. Sixty to 90 minutes after completion of the block, right auricular pressures were taken in six animals. In every case

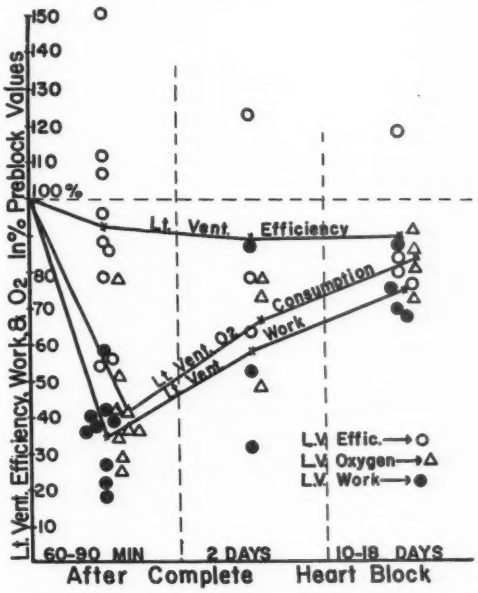

FIG. 7. Changes in left ventricular work, oxygen consumption, and efficiency at varying times after section of the bundle of His. Results are in per cent of preoperative values, each animal serving as his own control.

a small elevation of pressure occurred, ranging from 10 to 30 mm. saline. The right auricular pressure was recorded pre- and postoperatively in the four dogs followed 10 to 18 days, with pressure increases of 20, 20, 30, and 50 mm. saline.

The Influence of Miscellaneous Factors on Idioventricular Rate. The investigations of Erlanger[3] on the effects of acute asphyxia, acute exsanguinating arterial hemorrhage, and distal stimulation of the cut vagus nerve were repeated in 4, 3, and 2 dogs, respectively. In confirmation of the earlier work, significant rate changes were not noted with any of these procedures.

The Effect of Complete Heart Block on Heart Weight. At autopsy, 2 to 18 days after section of the bundle of His, various portions of the heart were weighed. In all cases the left ventricle was weighed after dissection by the method of Goodale and Hackel.[10] In three animals sacrificed after 48 hours, the left ventricular weight was essentially that predicted on the basis of body weight (fig. 8). In

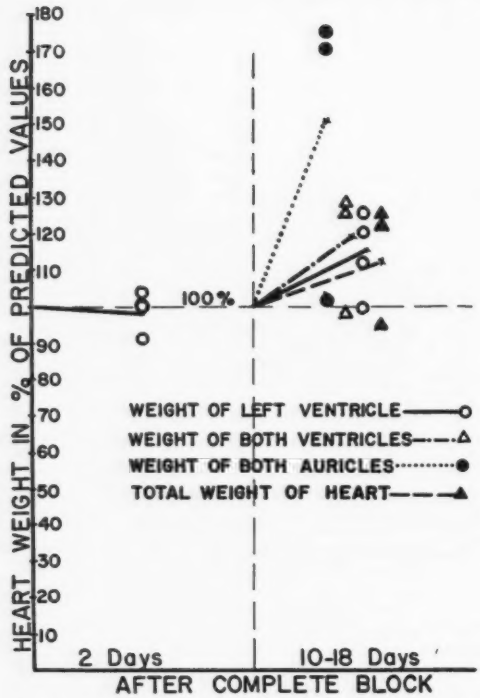

FIG. 8. Changes in heart weight. Note dogs sacrificed after 48 hours had no hypertrophy. Heart weights were abnormally high in animals sacrificed after 10 to 18 days. The percentage values were obtained by dividing the actual post mortem heart weights by the weights predicted on the basis of body weight.

the four animals sacrificed after 10 to 18 days, left ventricular weight was greater than predicted in three cases, with increases from 13 to 25 per cent. In three of the 10 to 18 day series, the total heart weight, weight of both auricles, and weight of both ventricles were also determined and the measures were compared with the values predicted by the method of Herrmann.[17] In two of these three dogs, the weight measures were greater than would have been expected in normal dogs (fig. 8), the exception being the animal which had similarly evidenced no left ventricular hypertrophy.

Autopsy Findings. In all animals kept for 48 or more hours, gross examination was conducted, and tissue kept for microscopic study. Except for myocardial hypertrophy (see above) no gross abnormalities were noted. The tricuspid valves were examined with care, since the section of the bundle of His was through the base of this valve. In all cases, injury to the tricuspid was either not present or trivial. All other valves were uninjured. In every case, sections of the myocardium, lung and liver were made. In one dog, which was sacrificed 12 days after surgery, equivocal evidence of early passive congestion of the liver was reported, but in all other cases the tissues were normal.

DISCUSSION

The present work, together with a companion chronic study,[8] permits the integrated outline of the natural history of complete heart block in dogs. Immediately, there is a reduction in cardiac output, coronary flow, and mean arterial pressure, with subsequent gradual return toward preblock values. Full compensation may never occur, in which case right and left sided congestive heart failure results.[8] Some dogs have an evident full restoration of cardiac reserve, but this usually requires several months.[8] In the present study, cardiac hypertrophy was not demonstrable after two days, but was present 10 to 18 days after induction of complete heart block. In the chronic study[8] in which all animals were studied at least six weeks after operation, every animal had cardiac hypertrophy.

SUMMARY

A study has been conducted on the effects of surgically induced complete heart block, acutely and for as long as 18 days postoperatively. Idioventricular rates ranged from 25 to 67 per minute. Immediately after the production of the lesion, cardiac output, coronary flow, and mean arterial pressure were reduced, in rough proportion to the degree of bradycardia. At this time the cardiac output could be restored to the preoperative levels by electrical stimulation of the ventricles at the same rate as had been present before the block.

The total oxygen consumption of animals with complete heart block remained essentially unchanged. With the minimally altered oxygen need, metabolic demands were met by an increased extraction of oxygen from the blood,

with a consequent widening of the arterial-venous difference.

With the passage of time, these measures gradually returned toward values which had been present before operation, although even at 18 days cardiac output, coronary flow, and mean femoral pressure were still low, and the arterial-venous difference widened. During this period, elevations in central venous pressure, of from 20 to 50 mm. water, occurred.

All animals observed for two days or longer were autopsied and histologic sections made of the liver and lungs. No gross abnormalities were detected. One dog had histologic evidence of early passive congestion of the liver. After 48 hours, myocardial hypertrophy was not present, but after 10 to 18 days increases in heart weight were found in three of four animals.

Summario in Interlingua

Le studio hic reportate esseva executate in canes durante un periodo de 18 dies comenciante immediatemente post le production chirurgic de complete bloco cardiac. Immediatemente post le operation, rendimento cardiac, fluxo coronari, e pression arterial median esseva reducite plus o minus in proportion con le grado de bradycardia. In le curso del tempore iste valores comenciava retornar verso le nivellos preoperative. Parallel al diminuite labor sinistro-ventricular il habeva un diminuite consumption sinistro-ventricular de oxygeno sin considerabile effecto super le efficacia myocardiac. Leve augmentos esseva constatate in le pression venose central. Al autopsia le sol anormalitate inequivoc esseva hypertrophia myocardiac que deveniva mesurabile a periodos de inter 2 e 18 dies post le operation.

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The Effect of Exercise on the Excretion of Water by Patients with Congestive Failure

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WITH THE TECHNICAL ASSISTANCE OF KATHERIN PONDER, B.S.

Some patients with congestive cardiac failure maintain hyponatremia by the excretion of only small amounts of hypertonic urine. In the present study it is shown that following exercise the experimentally overhydrated patient with congestive cardiac failure excretes a very small amount of urine which may be hypertonic. This is in accord with the hypothesis that events which increase the severity of failure increase the tendency to the development of hyponatremia.

SOME patients with congestive cardiac failure excrete small amounts of hypertonic urine even after the ingestion of water and thus develop hyponatremia.[1] Clinical observations have suggested that events which increase the severity of failure increase the tendency to the retention of water and the development of hyponatremia.[2, 3] The present study was carried out to determine if exercise, presumably by increasing the severity of failure, would cause this abnormality in the excretion of water to occur.

METHODS

Sodium[4] and urea[5] concentrations and freezing point depressions[6] were determined by methods reported in the literature. The concentrations of an ideal solute necessary to produce the observed depressions of freezing point were calculated and are reported as total solute in units of milliosmols per kilogram of water.[6] The venous pressure was measured by connecting a saline manometer directly to a needle inserted in an antecubital vein. With the patient reclining the venous pressure was recorded as the height of the saline above a plane halfway between the uppermost portion of the sternum and the back of the patient.

PROCEDURE

Each subject had nothing by mouth for nine hours prior to the observations. Venous pressure was determined at 8:45 a.m. At 9:00 a.m. the subject ingested 5 to 10 ml. of water per kilogram of body weight at 30-minute intervals for four doses, a total of 20 to 40 ml. per kilogram. The subject sustained the water load throughout the observations by ingesting water in an amount equal to the urinary output. Urine was obtained by having the patient stand and void. At 11:00 a.m. urine collections were begun. In some studies urine was collected for six 15-minute periods with the subject lying down. In the other studies urine was collected during two control periods, during an exercise period, and during two to four recovery periods. The periods were usually 15 minutes in length. However, in some cases very low rates of urine flow made periods up to 30 minutes necessary. During the control and recovery periods the subjects lay in bed. During the exercise periods the normal subjects walked at 4 miles per hour on a level walkway for 14 minutes. An attempt was made to have the patients walk at this rate. They were unable to do so and walked at a somewhat slower rate. Most of them were prevented from completing a full 14 minutes of exercise by the development of dyspnea or fatigue. Blood was drawn at 8:45 a.m., 10:45 a.m. and at the completion of the study.

SUBJECTS

Six men with cardiac disease, all of whom had been in severe congestive failure, and two normal men were studied. The ages and specific diagnoses are given in tables 1 and 2. At the time of the studies all of the patients had been treated with digitalis, low sodium diets and mercurial diuretics. Four patients were free of edema and had normal venous pressures. Two patients had slight pedal edema and increased venous pressures as recorded in table 2. Each of the patients accumulated edema whenever the dietary restriction of sodium and the use of

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TABLE 1.—*Effect of Exercise on Excretion of Water and Solutes by a Normal Man**

Experiment	Time† min.	Urine Flow ml./min.	Urinary Total Solute Concentration mOsm./Kg.H_2O	Urinary Urea Excretion mM/min.	Urinary Na Excretion mEq./min.	Serum Total Solute Concentration mOsm./Kg.H_2O	Serum Na Concentration mEq./L.
Water Load	−120					286	141
40 ml./Kg.	0–15	9.1	92	.328	.110	273	136
	15–30	8.5	91	.323	.094		
No Exercise	30–45	8.0	82	.336	.080		
	45–60	8.3	83	.340	.088		
	60–75	8.3	84	.374	.095		
	75–90	8.3	85	.340	.098	272	133
Water Load	−120					288	143
40 ml./Kg.	0–15	7.6	99	.274	.089	272	133
	15–30	7.9	98	.292	.094		
Walked 14 min.	30–45‡	6.3	93	.277	.066		
	45–60	7.3	93	.307	.082		
	60–75	6.4	93	.282	.072		
	75–90	6.4	98	.301	.083		
	90–105	6.3	94	.296	.078	271	136

* 35 yrs. old. Venous pressure 100 mm. of water.

† Hydration started at −120 minutes.

‡ The period in which exercise occurred is underlined.

mercurial diuretics were discontinued. They were all ambulatory and free of symptoms except on exertion. Blood pressures and the results of clinical urinalyses were normal.

RESULTS

Data from representative studies are given in tables 1 and 2 and are illustrated in figures 1 to 3. Ingestion of from 20 to 40 ml. of water per kilogram of body weight was followed by a reduction in the total solute and sodium concentrations of the serum and the establishment of an increased flow of dilute urine.

The course of water diuresis without exercise was observed in three studies of two normal men. Following the establishment of diuresis, the rates of excretion of water, sodium and urea remained almost constant or decreased slightly. The urinary total solute concentration remained almost constant.

The effect of exercise on water diuresis by normal man was observed in four studies on two normal men (table 1, fig. 1). Walking at approximately 4 miles per hour for 14 minutes was accompanied by only small changes in the course of the diuresis. The rates of excretion of water, sodium and urea always decreased slightly. The total solute concentration remained almost constant.

The effect of exercise on water diuresis by the patient with congestive cardiac failure was studied in 6 patients (table 2). Walking at somewhat less than 4 miles per hour for 6 to 14 minutes greatly decreased the rates of excretion of water, sodium and urea by all these patients. In three cases (C. S., H. Z., and J. C.) the urinary total solute concentration changed relatively little (fig. 2). In the other three cases (R. W., W. L., and C. K.) the urinary total solute concentration increased much more following exercise. In two of these three cases the urinary total solute concentration exceeded the serum total solute concentration (fig. 3).

DISCUSSION

The excretion of water and solutes by the normal subjects changed very little following exercise. The severity of the exercise was apparently insufficient to produce the more definite decreases in water and sodium excretion which have been reported for normal subjects by others.[7, 8, 9]

TABLE 2.—*Effects of Exercise on Excretion of Water and Solutes by Patients with Congestive Failure*

Subject	Time* Min.	Urine Flow ml./min.	Urinary Total Solute Concentration mOsm./Kg. of H_2O	Urinary Urea Excretion mM/min.	Urinary Na Excretion mEq./min.	Serum Total Solute Concentration	Serum Na Concentration
Pt. C. S. 52 yr. old	−120					283	142
M. S.	0–15	11.5	101	.460	.274	268	133
40 ml. H_2O/Kg.	15–30	13.9	104	.514	.324		
Walked 6 min.	30–45†	2.7	104	.127	.040		
V. P. 105 mm. H_2O	45–60	3.7	118	.274	.003		
No edema.	60–75	4.9	121	.353	.026		
	75–90	7.9	114	.458	.126	267	132
Pt. H. Z. 42 yr. old	−120					284	139
A. S.	0–15	8.8	105	.299	.088	280	136
20 ml. H_2O/Kg.	15–30	7.3	109	.270	.058		
Walked 10 min.	30–45	3.5	115	.133	.028		
V. P. 50 mm. H_2O	45–60	3.0	122	.147	.018		
No edema.	60–75	6.9	114	.276	.055		
	75–90	6.9	113	.290	.076	277	136
Pt. J. C. 72 yr. old	−120					284	139
A.S.H.D.	0–15	11.2	78	.504	.020	269	131
30 ml. H_2O/Kg.	15–30	5.2	79	.484	.010		
Walked 14 min.	30–45	2.7	97	.170	.003		
V. P. 110 mm. H_2O	45–60	4.3	125	.361	.003		
No edema.	60–75	7.7	87	.454	.007		
	75–90	7.3	81	.394	.006	269	133
Pt. R. W. 59 yr. old	−120					272	132
A.S.H.D.	0–15	6.4	58	.224	.006	261	128
40 ml. H_2O/Kg.	15–30	6.1	51	.201	.006		
Walked 10 min.	30–60	.8	114	.038	.004		
V.P. 195 mm. H_2O	60–75	.2	259		.001		
Slight edema.	75–90	2.0	178	.198	.003		
	90–105	5.6	97	.308	.005		
	105–120	8.5	53	.306	.006	261	126
Pt. W. L. 63 yr. old	−120					294	142
A.S.H.D.	0–17	3.8	226	.467	.003	275	133
40 ml. H_2O/Kg.	17–31	5.4	209	.621	.004		
Walked 13 min.	31–54	1.4	235	.181	.002		
V.P. 170 mm. H_2O	54–78	1.9	353	.355	.003		
Slight edema.	78–108	1.9	359	.393	.002	274	135
Pt. C. K. 23 yr. old	−120					281	141
M.S.	0–16	5.8	90	.290	.030	267	136
40 ml. H_2O/Kg.	16–30	6.4	89	.314	.035		
Walked 11 min.	30–50	.5	112	.030	.004		
V.P. 120 mm. H_2O	50–61	.6	346	.079	.026		
No edema.	61–75	.9	520	.149	.055		
	75–90	1.1	426	.172	.057		
	90–105	1.5	354	.218	.066	262	133

* Hydration started at −120 minutes.

† The period in which the exercise occurred is underlined.

A.S.—Aortic stenosis M.S.—Mitral stenosis

A.S.H.D.—Arteriosclerotic heart disease V.P.—Venous pressure

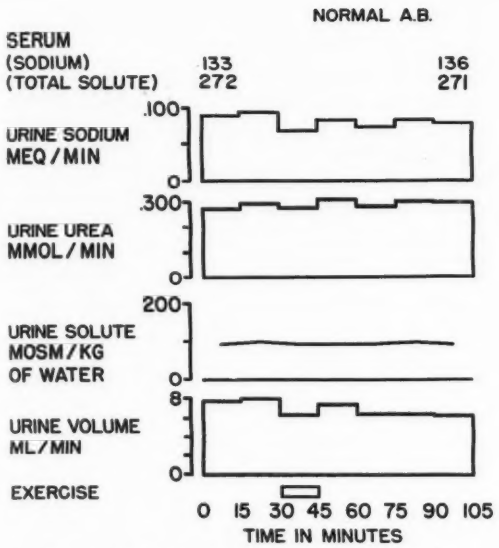

FIG. 1. The effect of exercise on the excretion of water and solutes by a hydrated normal man. Zero time is 120 minutes after the beginning of hydration. Serum sodium and total solute concentrations are given at the top of the figure. Their concentrations prior to hydration were 143 mEq./L. and 288 mOsm./Kg. of water respectively.

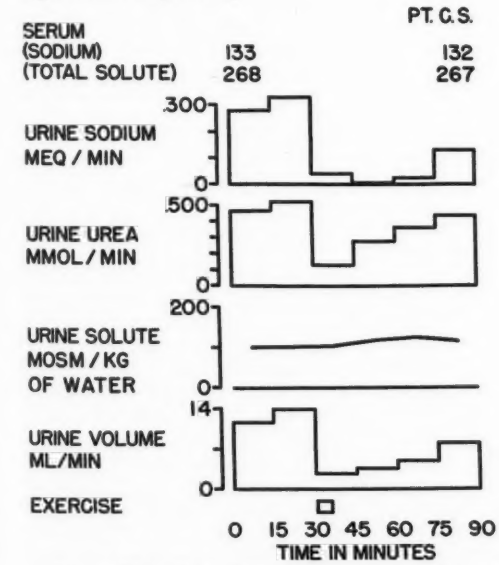

FIG. 2. The effect of exercise on the excretion of water and solutes by a hydrated man with mitral stenosis and congestive failure. Serum sodium and total solute concentrations prior to hydration were 142 mEq./L. and 283 mOsm./Kg. of water.

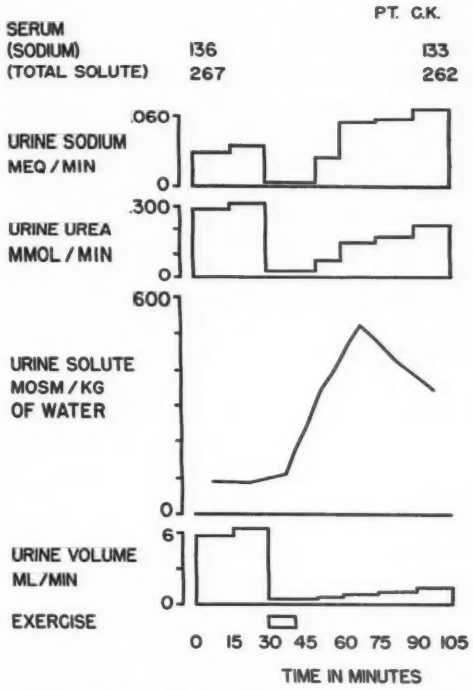

FIG. 3. The effect of exercise on the excretion of water and solutes by a hydrated man with mitral stenosis and congestive failure. Serum sodium and total solute concentrations prior to hydration were 141 mEq./L. and 281 mOsm./Kg. of water.

However, even milder exercise produced large decreases in the urinary excretion of water, sodium and urea by the patients with congestive cardiac failure. Such a decrease in water and sodium excretion during exercise by patients with cardiac disease has been previously reported.[10] In the present study the errors in the estimation of sodium and urea excretion introduced by the greatly reduced water excretion should be considered. When urinary flow decreases, the excretion of a given solute for a given period is underestimated if there is a rise in the concentration of that solute in the urine leaving the renal tubules and entering the proximal portion of the renal "dead space." An estimate of this concentration for each solute was obtained from the concentration of that solute in the urine collected later in each experiment. In each case in which there was little change in the urinary

total solute concentration (C. S., H. Z., and J. C.) the sodium concentration fell following exercise. Thus error due to "dead space" led to an underestimate of the magnitude of the decrease in the excretion of sodium. In these same cases the errors introduced by changes in urea concentration were relatively small. However, the errors introduced into the estimation of the rates of excretion of sodium and urea in the cases (R. W., W. L., and C. K.) in which the urinary total solute concentration rose greatly, were large enough to prevent any precise interpretation of these data.

The decreases in water and solute excretion without much change in total solute concentration were presumably due to decreased glomerular filtration rate[11] and possibly to increased isosmotic reabsorption of solute and water. The increased urinary total solute concentration observed in three cases may have been due to the action of neurohypophyseal antidiuretic hormone. The possibility that an extreme reduction in glomerular filtration rate may have led to the formation of hypertonic urine even in the absence of antidiuretic hormone cannot be excluded.

The ingestion of water produced definite hyponatremia in all the patients. Those who excreted a greatly reduced volume of hypertonic urine as a result of exercise resembled for a brief period patients in congestive failure who maintain hyponatremia chronically by the excretion of only small volumes of hypertonic urine. This result is in accord with the concept that the maintenance of hyponatremia by patients with congestive cardiac failure may be a manifestation of increased severity of failure.[2, 3]

Summary

Exercise of a degree which produced little or no change in the renal excretion of water by normal subjects caused great reduction in excretion of water by patients with congestive cardiac failure who had ingested enough water to produce hypotonicity of the serum and hyponatremia.

In some instances this reduction of renal excretion of water was accompanied by the production of a hypertonic urine.

Possible mechanisms of these phenomena and their relation to the hyponatremia which occurs spontaneously in congestive failure are discussed.

Summario in Interlingua

Exercitio a un grado que habeva pauc o nulle effecto super le excretion renal de aqua in individuos normal causava un grande reduction del excretion renal de aqua in patientes con dysfunctionamento cardiac congestive, ben que illes habeva ingerite satis aqua pro producer hypotonicitate del sero e hyponatremia.

In alicun casos iste reduction del excretion renal de aqua esseva accompaniate per le production de urina hypertonic.

Es discutite le possibile mechanismos de iste phenomenos e lor relation al hyponatremia que occurre spontaneemente in dysfunctionamento congestive.

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Renal Hemodynamic Response to Vasopressor Agents in the Treatment of Shock

By JOHN H. MOYER, M.D., GEORGE MORRIS, M.D. AND H. LISTON BEAZLEY, M.D.

Norepinephrine, when administered to normotensive subjects by continuous intravenous infusion produces a marked renal vasoconstriction and a reduction in renal blood flow. The opposite response is observed when this drug is given to patients in whom glomerular filtration rate and renal blood flow are already depressed due to shock. When the blood pressure in these patients is returned to normal with norepinephrine, there is an increase in both glomerular filtration rate and renal blood flow. There is also an increase in water and electrolyte excretion which is secondary to the increase in glomerular filtration rate.

ALTHOUGH vasopressor agents have been advocated for the treatment of shock, very few observations have been made on the hemodynamic responses of critical vascular beds to these compounds. Recently we have observed that when patients are made hypotensive with ganglionic blocking agents, blood flow through the kidneys and brain is reduced.[1, 2] When these same subjects are then rendered normotensive with vasopressor agents, the blood flow to these organs rapidly approaches the control observations.[2, 3] Although not analogous to shock, these observations present a paradox since if vasopressor agents are administered to normal subjects and the blood pressure raised to hypertensive levels, blood flow through the kidneys is reduced.[4] These apparently confusing observations suggest a need for a better understanding of the pharmacodynamics of vasopressor agents when used either as primary treatment of hypotension or as an adjunct to other measures used in the treatment of shock. The current observations were made in order to assess the renal functional response to vasopressor agents when used for the treatment of shock due to numerous causes.

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Supported in part from the Medical Research and Development Board, Office of the Surgeon, Department of the Army, under contract number DA-49-007-MD 314, and the National Institutes of Health, U. S. Public Health Service.

MATERIAL AND METHODS

The patients in this study are divided into two groups. The first group was composed of patients admitted to the emergency room of a city-county hospital with untreated hemorrhagic and traumatic shock for which they received norepinephrine or Aramine (levo 1-(m-hydroxyphenyl)-2-amino-1-propanol). The second group consisted of hospitalized patients who received a vasopressor agent for the treatment of normovolemic shock due to numerous causes.

Renal function was determined, using inulin clearance as a measure of glomerular filtration rate (GFR) and low concentrations (2 to 4 mg. per 100 cc.) of para-aminohippurate (PAH) to measure renal plasma flow, methods and techniques previously described being used.[5, 6] In the normovolemic group who were already being treated with a continuous infusion of norepinephrine, the norepinephrine was discontinued long enough to obtain two or three 10-minute collection periods during hypotension. These were designated as the control observations. Norepinephrine infusion was then restarted and a variable number of additional 10-minute collection periods obtained.

In the hemorrhagic and traumatic cases, 1,000 to 1,500 cc. of 5 per cent glucose in water were given rapidly (intravenously) on arrival in the emergency room in order to insure satisfactory hydration for maximum urine formation under the circumstances. One to three 10-minute collection periods were then obtained while the patient was in shock. Patients who obtained a marked improvement in their clinical status on administration of the infusion of 5 per cent glucose, were discarded from the study. This served to eliminate patients who were border line and not seriously shocked. One such patient (T. H.-286—tables 1 to 4) is included for comparative purposes. Following the control observations two to six 10-minute periods were obtained during norepinephrine or Aramine induced normotension.

TABLE 1A.—*Summary of Clinical Data on Patients Treated*

Patient	Age	Race and Sex	Diagnosis	Etiology of Shock	Complicating Factors	Clinical Results
Group 1—Patients with Shock Due to Hemorrhage						
R. D.-280	31	N/M	Lac. l. forearm	Blood loss	None	Recovered
W. H.-281	38	W/M	Mult. lac. scalp	Blood loss	None	Recovered
M. C.-282	45	W/M	Idiopath. gastric hem.	Blood loss	Massive hem.; unable to restore blood vol.	Subtotal gastrect.; given 15,000 cc. blood. Died next day.
E. B.-283	36	N/M	Lac. ulnar art.	Blood loss	None	Recovered
L. M.-284	52	N/F	Hemopneumothorax. Mult. rib fract.	Trauma	Severe alcohol.	Recovered
V. S.-285	44	W/F	Portal cirrh.	Bleeding esoph. varices	Jaundice	Developed hepatic coma. Died in 48 hrs.
T. H.-286	39	N/M	Stab wound shoulder	Alcohol. & min. blood loss	Alcohol.	Recovered
Group 2—Patients with Normal Volume Shock						
G. W.-287	70	W/M	Perforated gastric ulcer	Bile peritonitis	Closure leaked	Died in 4 days
L. H.-289	29	N/F	Criminal abortion	Intrauterine Lysol	Renal tub. necrosis	Recovered
J. N.-290	70	N/M	Ca. prostate	Mult. bony metastases. Terminal ca.	Metastases. No Uremia	Died in 4 days
V. W.-291	24	N/F	Postpartum—triplets	Postpartum—triplets	Schizophrenia	Recovered
G. H.-292	51	W/F	Cirrh., chr. pyeloneph., uremia	Hepatic coma	Chr. alcohol., dehydration	Died following day
J. M.-293	44	W/M	Lymph. leukemia	Electrolyte imbal. Plasma K = 2.2 mEq.		Recovered from shock in 24 hrs. after K corrected
D. L.-294	53	W/M	Myo. infarct.	Cardiogenic	None	Recovered
T. R.-295	63	W/M	Myo. infarct.	Cardiogenic	Heart fail.	Died after 18 hrs. of therapy

Lac. = laceration.
Cirrh. = cirrhosis.
Pyeloneph. = pyelonephritis.
Lymph. = lymphatic.

The vasopressor agent was then discontinued and two more periods were collected after the blood pressure had again returned to shock levels. Following these observations, blood had become available and the patient was then transfused. Three to six more collection periods were obtained after stabilization of vital signs following the blood transfusion. In several cases follow-up studies were done after 24 hours or more. Mean arterial blood pressure was calculated by adding one-third of the pulse pressure to the diastolic pressure.

RESULTS

The clinical observations on the patients of both groups I and II are summarized in tables 1A and 1B. There were seven patients who suffered from hemorrhagic shock (group I) and eight patients who were in shock from causes other than blood loss (group II). It is to be noted that the general status of the patients in group II was far worse than it was in those

TABLE 1B.—*Summary of Clinical Data on Patients Treated*

Patient	Vasopressor Agent	Dose in micro-gm./min.	Previous Therapy
Group 1—Patients with Shock due to Hemorrhage			
R. D.-280	Norepineph.	20	1200 cc. 5% glu. in H_2O
W. H.-281	Norepineph.	32	1000 cc. 5% glu. in H_2O
M. C.-282	Aramine	200	1000 cc. 5% glu. in H_2O
E. B.-283	Norepineph.	18	1000 cc. 5% glu. in H_2O
L. M.-284	Norepineph.	30	1000 cc. 5% glu. in H_2O
V. S.-285	A-Aramine B-Norepi-neph.	528 25	Esoph. balloon inserted just prior to study
T. H.-286	Norepineph.	22	1500 cc. 5% glu. in H_2O
Group 2—Patients with Normal Volume Shock			
G. W.-287	Norepineph.	12	Simple closure 48 hours previously
L. H.-289	Norepineph.	84	500 cc. blood, DOCA, cortisone, glu. in H_2O (2000 cc.)
J. N.-290	Norepineph.	22	Orchidect. T.U.R. 10 days before
V. W.-291	Norepineph.	17	None
G. H.-292	Norepineph.	96	2000 cc. blood. I.V. fluids
J. M.-293	Norepineph.	19	Nitrogen mustard. Blood and I.V. crystaloids
D. L.-294	Norepineph.	4	Sedation
T. R.-295	Norepineph.	32	Sedation

Glu. = glucose.
T.U.R. = transurethral resection.

patients in group I. Had not another complication developed, all of the patients in group I would probably have recovered.

The effect of vasopressor agents on renal hemodynamics is summarized in table 2. The renal vascular resistance was increased in patients with hemorrhagic shock as well as in the patients with nonhemorrhagic shock. Although blood pressure prior to vasopressor therapy was depressed to about the same extent in both groups of patients, renal blood flow was more markedly depressed in the patients with nonhemorrhagic shock. This was probably due to the very poor condition of the patients in the latter group. The difference between the two groups in renal hemodynamic response to vasopressor agents is even more outstanding. In the patients with shock due to blood loss (group I), when the blood pressure was increased with the vasopressor agent glomerular filtration rate returned to or toward normal (table 3) and renal blood flow increased markedly in most of the patients (table 2). Although the renal blood flow and glomerular filtration rate increased, they did not return to within normal ranges in any of the patients with normovolemic shock. Likewise, the renal vascular resistance which was increased prior to therapy frequently did not decrease when norepinephrine was administered. Even patients with primary renal damage usually showed some improvement in function. One such example was patient 289—L. H. who suffered from renal damage due to Lysol administration. She showed a slight increase in renal blood flow when the blood pressure was increased with norepinephrine.

The effect of increasing the blood pressure with norepinephrine on glomerular filtration rate is summarized in table 3. There was a close parallel between the effect on glomerular filtration rate and renal blood flow. Glomerular filtration rate returned to or towards normal ranges in all but one of the patients in group I. By contrast, glomerular filtration rate did not increase to normal values in any of the patients in group II, although it increased somewhat in all of the patients, even in the patient (L. H.) with renal tubular necrosis.

When the vasopressor agents were discontinued prior to the administration of blood to the patients in group I, renal function was usually depressed again to a point approximating the observations made during the control periods. When compared with the control observations, both glomerular filtration rate and renal blood flow increased following blood transfusions in all of the patients in this group. It was quite a surprise to note that the immediate responses of glomerular filtration rate and renal

TABLE 2.—*Renal Hemodynamic Response to Vasopressor Agents During Shock*

Patient	Mean Blood Pressure mm. Hg					Renal Blood Flow ml/min.					Renal Vascular Resistance*					Hematocrit					Volume of Blood Transfusion
	C	V_1	V_2	B_1	B_2	C	V_1	V_2	B_1	B_2	C	V_1	V_2	B_1	B_2	C	V_1	V_2	B_1	B_2	
Group 1—Hemorrhagic Shock																					
R. D.-280	17	72	93	98	91	303	1248	1717	1159	1125	.06	.06	.05	.08	.08	36	36	35	41	40	1000 cc.
W. H.-281	64	86	89	91‡	103	14	720	1321	358†	—‡	4.57	.12	.09	.25	—‡	30	30	30	35	33	1000 cc.†
M. C.-282	64	73	84	84‡	—	122	245	550	548†	—	.52	.30	.15	.15	—	26	26	28	35	—	2500 cc.†
E. B.-283	50	85	95	99	—	126	1188	1320	1838	—	.40	.07	.07	.05	—	39	40	40	47	—	1000 cc.
L. M.-284	43	76	85	76	83	—§	340	681	850	868	—§	.22	.12	.09	.10	25	25	28	28	38	500 cc.
V. S. 285A	42	52	74	—	—	—§	1291	1627	—	—	—§	.04	.05	—	—	38	33	33	—	—	1000 cc.
V. S.-285B	58	67	72	77	—	331	561	593	746	—	.18	.12	.12	.10	—	38	33	33	39	—	2000 cc.
T. H.-286‖	83	98	105	100	—	1266	1178	1120	1693	—	.07	.08	.09	.06	—	35	35	35	40	—	500 cc.
Group 2—Non-hemorrhagic Shock of Varied Etiology																					
G. W.-287	83	—	101	—	—	118	—	274	—	—	.70	—	.37	—	—	50	—	50	—	—	None
L. H. -289	57	—	98	—	83	53	—	195	—	483	1.08	—	.93	—	.17	40	—	40	—	30	None
J. N.-290	67	89	110	—	—	347	404	403	—	—	.19	.22	.27	—	—	28	28	25	—	—	None
V. W.-291	53	86	112	—	97	69	106	220	—	255	.77	.81	.51	—	.38	48	50	50	—	24	None
G. H.-292	37	74	92	—	—	23	40	38	—	—	1.61	1.85	2.42	—	—	27	27	27	—	—	None
J. M.-293	37	69	92	—	—	5	633	897	—	—	—	.11	.10	—	—	40	40	42	—	—	None
D. L.-294	49	—	72	—	71	293	—	634	—	821	.17	—	.11	—	.09	42	—	41	—	44	None
T. R.-295	19	—	78	—	77	76	—	190	—	55	.25	—	.41	—	—	50	—	48	—	56	None

C—Control during shock.

V_1—Partial restoration of blood pressure with a vasopressor agent.

V_2—Complete restoration of blood pressure with a vasopressor agent.

B_1—Immediately after transfusion of blood.

B_2—Follow-up study completed. R. D., 24 hours after B_1; W. H., 5 days after B_1; L. M., 24 hours after B_1; L. H., 25 days after V_2; V. W., 6 days after V_2; D. L., 6 hours after V_2.

* Renal Vascular Resistance $\pm \frac{\text{Mean Blood Pressure}}{\text{Renal Blood Flow}}$.

† Insufficient blood replacement at time of study, transferred to surgery.

‡ Sulfa drug therapy interfered with PAH determinations.

§ Undeterminable due to extremely low PAH clearance.

‖ Patient clinically in shock but blood pressure was normal following the infusion of 1500 cc. of 5% glucose. Renal functions were not depressed

blood flow to blood transfusions were frequently not as great as the responses to vasopressor agents.

During shock due to hemorrhage and other causes, urine volume and the excretion rates of sodium and potassium were markedly depressed. As the blood pressure was increased there was a sharp increase in both water and sodium excretion. This was probably a reflection of the increase in glomerular filtration rate. Even in the patient with tubular necrosis, there was an increase in sodium and water excretion even though glomerular filtration rate did not increase above 30 cc. per minute which is about one-fourth of the normal value. In the patients with shock due to hemorrhage, blood transfusions appeared to increase sodium excretion more than norepinephrine did. There was usually a parallel increase in potassium excretion.

CASE REPORTS

The following cases are given in more detail because they present pertinent points in the study.

Patients in shock due to blood loss and trauma (group I)

Case 1. R. D., a patient with moderate hemorrhagic shock. This patient was a 31-year old Negro man who had an extensive laceration of the arm. His systolic blood pressure was 50 mm. Hg. after the rapid instillation of 1,200 cc. 5 per cent glucose in water. The diastolic pressure was not obtainable. Renal function was restored to normal levels with norepinephrine. Comparable values were obtained after restoration of blood volume with 1,000 cc. blood. The laceration was repaired and recovery was uneventful (tables 1 to 4).

Case 2. W. H. Patient W. H., a typical case of shock due to hemorrhage and lacerations of the scalp. This patient illustrates the response from a moderate degree of hemorrhagic shock. He was a

TABLE 3.—*Effect of Vasopressor Agents During Shock on Glomerular Filtration Rate and Renal Plasma Flow*

Patient	Glomerular Filtration Rate‖ ml/min.					Renal Plasma Flow‖ ml/min.					Filtration Fraction*				
	C	V_1	V_2	B_1	B_2	C	V_1	V_2	B_1	B_2	C	V_1	V_2	B_1	B_2
Group 1—Hemorrhagic Shock															
R. D.-280	29	43	115	119	103	194	799	1116	684	675	.15	.05	.10	.17	.15
W. H.-281	3	114	92	67†	155	10	504	715	233†	—‡	.30	.23	.13	.29	—†
M. C.-282	10	60	78	82†	—	90	181	396	356†	—	.11	.33	.20	.23	—
E. B.-283	11	86	85	78	—	77	713	792	974	—	.14	.12	.11	.08	—
L. M.-284	—§	5	16	23	119	—§	255	490	612	538	—§	.02	.03	.04	.22
V. S.-285A	—§	66	94	—	—	—§	865	1090	—	—	—§	.08	.09	—	—
V. S.-285B	31	53	58	48	—	205	376	397	455	—	.15	.14	.15	.11	—
T. H.-286	128	137	140	184	—	823	766	728	1016	—	.16	.18	.19	.18	—
Group 2—Non-hemorrhagic Shock of Varied Etiology															
G. W.-287	5	—	15	—	—	59	—	137	—	—	.08	—	.11	—	—
L. H.-289	9	—	25	—	87	32	—	63	—	338	.28	—	.40	—	.26
J. N.-290	33	38	38	—	—	250	291	302	—	—	.13	.13	.13	—	—
V. W.-291	3	10	12	—	44	36	53	110	—	194	.08	.19	.11	—	.23
G. H.-292	5	11	12	—	—	17	29	28	—	—	.29	.38	.43	—	—
J. M.-293	3	31	69	—	—	3	330	520	—	—	1.00	.08	.13	—	—
D. L.-294	48	—	86	—	88	170	—	374	—	460	.28	—	.23	—	.19
T. R.-295	12	—	37	—	14	38	—	99	—	24	.32	—	.37	—	.58

C—Control during shock.

V_1—Partial restoration of blood pressure with a vasopressor agent.

V_2—Complete restoration of blood pressure with a vasopressor agent.

B_1—Immediately after transfusion of blood.

B_2—Follow-up study—R. D., 24 hours after B_1; W. H., 5 days after B_1; L. M., 24 hours after B_1; L. H., 25 days after V_2; V. W., 6 days after V_2; D. L., 6 hours after V_2.

* Filtration Fraction $= \frac{\text{Glomerular Filtration Rate}}{\text{Renal Plasma Flow}}$.

† Insufficient blood replacement at time of study.

‡ Sulfa drug therapy interfered with PAH determinations.

§ Undeterminable due to extremely low inulin and PAH clearance.

‖ Normal values for glomerular filtration rate in this laboratory are 100 to 140 cc per minute and for renal plasma flow are approximately 600 to 800 cc per minute.

38-year old white man who had multiple lacerations of the head and a mean blood pressure prior to treatment of 52 to 60 mm. Hg. He was given 1,000 cc. of 5 per cent glucose in distilled water which did not affect his blood pressure appreciably. Following norepinephrine infusion sufficient to restore mean blood pressure to a range of 85 to 90 mm. Hg, both renal blood flow and glomerular filtration rate were restored to nearly normal levels. After an increase in the blood volume with 1,000 cc. of blood the mean blood pressure ranged from 89 to 93 mm. Hg and glomerular filtration rate increased almost to normal, but renal blood flow remained depressed. This was probably due to inadequate blood replacement. His initial blood volume, while in shock immediately after the rapid infusion of 1,000 cc. 5 per cent glucose in water, was 4,519 cc. which may be high due to the temporary presence of a large portion of the crystaloid infusion in the vascular compartment. Five days later his blood volume was 5,740 cc. and his glomerular filtration rate was in the high normal range. Due to an intercurrent infection, the patient was given sulfonamide. As a result, it was not possible to determine renal blood flow during the follow-up study since sulfonamides interfere with the chemical analysis of para-aminohippurate.

As the glomerular filtration rate increased with both the vasopressor agent and the blood transfusion, there was a sharp increase in urine volume (fig. 1B). This was associated with a moderate initial and sustained increase in sodium and potassium excretion. The increase in sodium excretion was more marked after blood replacement than after blood pressure elevation with the vasopressor agent.

TABLE 4.—*Effect of Vasopressor Agents During Shock on Water and Electrolyte Excretion*

Patient	Urine Volume ml/min.					Plasma Sodium mEq/L					Plasma Potassium mEq/L					Sodium Excretion mEq/min.					Potassium Excretion mEq/min.				
	C	V_1	V_2	B_1	B_2	C	V_1	V_2	B_1	B_2	C	V_1	V_2	B_1	B_2	C	V_1	V_2	B_1	B_2	C	V_1	V_2	B_1	B_2
Group 1—Hemorrhagic Shock																									
R. D.-280	1.0	1.2	1.6	2.8	0.9	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
W. H.-281	0.1	0.8	0.8	0.8*	.6	130	128	128	133	134	2.8	3.2	3.2	4.0	4.3	8	20	19	25*	451	11	56	67	97*	46
M. C.-282	0.7	2.3	2.8	3.0*	—	135	127	127	123	—	4.4	4.9	4.8	5.7	—	39	179	192	188*	—	18	93	104	38*	—
E. B.-283	0.2	0.8	2.4	1.1	—	139	139	—	139	—	4.9	4.9	5.1	4.5	—	—	—	—	—	—	2	56	63	75	—
L. M.-284	0.0	1.0	2.4	1.6	3.3	135	135	131	125	123	3.6	3.2	3.2	2.9	3.3	0	61	152	663	108	0	27	53	55	33
V. S.-285A	0.0	0.4	1.4	—	—	138	138	135	—	—	3.8	3.7	3.6	—	—	0	3	16	—	—	0	2	67	—	—
V. S.-285B	0.7	0.7	0.8	1.2	—	137	—	136	138	—	3.8	—	3.5	3.5	—	3	4	5	4	—	20	36	45	66	—
T. H.-286	0.6	1.1	5.1	12.6	—	136	135	135	136	—	3.6	3.9	3.9	3.8	—	124	114	129	276	—	32	41	40	45	—
Group 2—Non-hemorrhagic Shock																									
G. W.-287	0.1	—	0.9	—	—	130	—	—	—	—	4.4	—	—	—	—	7	—	17	—	—	29	—	55	—	—
L. H.-289	0.4	—	1.9	—	5.7	143	—	124	—	133	3.4	—	2.8	—	3.9	18	—	87	—	157	1	—	3	—	38
J. N.-290	0.8	1.5	4.9	—	—	124	—	120	—	—	3.8	—	3.6	—	—	30	58	34	—	—	38	59	59	—	—
V. W.-291	0.2	0.6	0.6	—	2.6	130	—	124	—	151	5.1	—	4.8	—	3.0	9	10	17	—	62	8	8	14	—	22
G. H.-292	1.4	4.0	4.4	—	—	—	—	—	—	—	—	—	—	—	—	59	205	208	—	—	6	23	19	—	—
J. M.-293	0.2	1.5	6.2	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
D. L.-294	0.4	—	1.6	—	—	143	—	141	—	—	4.3	—	3.9	—	—	40	—	300	—	—	24	—	36	—	—
T. R.-295	0.2	—	0.8	—	0.3	143	—	140	—	138	4.6	—	4.0	—	3.8	21	—	82	—	16	26	—	30	—	17

C—Control during shock.

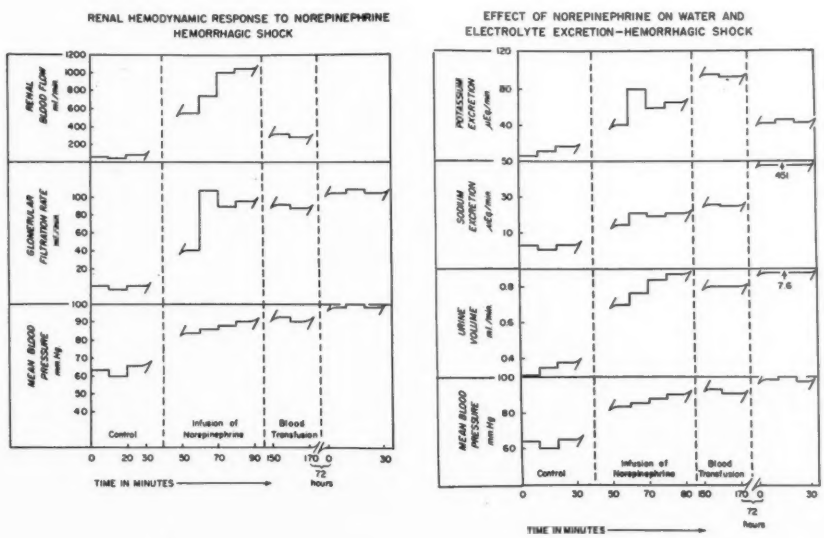
V_1—Partial restoration of blood pressure with a vasopressor agent.

V_2—Complete restoration of blood pressure with a vasopressor agent.

B_1—Immediately after transfusion of blood.

B_2—Follow-up study—R. D., 24 hours after B_1; W. H., 5 days after B_1; L. M., 24 hours after B_1; L. H., 25 days after V_2; V. W., 6 days after V_2; D. L., 6 hours after V_2.

* Insufficient blood replacement at time of study.



A *B*

FIG. 1. (*A*). A typical renal hemodynamic response to a vasopressor agent and to blood replacement in a patient with shock due to blood loss. In this instance, renal blood flow did not return to normal following the blood transfusion probably because of inadequate blood replacement. (*B*). Typical response of water and electrolyte excretion to vasopressor agent and to blood transfusion in a patient in shock due to blood loss. (Patient W. H.)

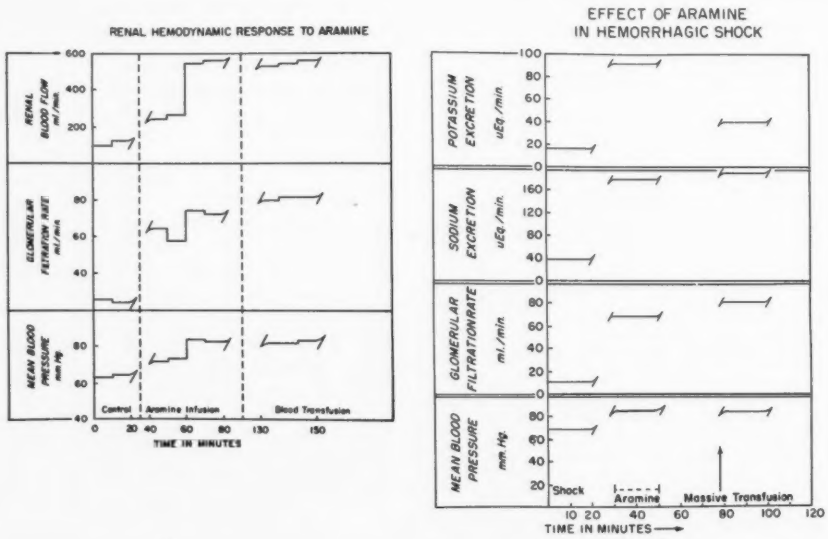
The following case represents the response to Aramine, a vasopressor agent which is longer acting than norepinephrine.

Case 3. M. C. A 45-year old white man was admitted to the Receiving Ward, having vomited an estimated 2 quarts of blood due to gastrointestinal hemorrhage. He have no history of peptic ulcer. His blood pressure was 70/50, the pulse rate was 120, and other clinical manifestations of shock were evident. The patient was given 1,000 cc. of 5 per cent glucose in water. Following the control observations on renal function, an infusion of Aramine in a concentration of 200 mg. per liter was started. There was a gradual increase in blood pressure to 104/76. This was associated with sharp increases in glomerular filtration rate and renal blood flow from about 10 per cent of normal values to about two-thirds and one-half of normal, respectively. After the observations on renal function were complete, the Aramine was discontinued and the patient was given 2,500 cc. of blood. The glomerular filtration rate and renal blood flow remained about the same as they had been during the Aramine infusion. However, the patient continued to bleed and he was taken to the surgical service where a gastrectomy was performed. Soon thereafter he again developed shock and it became necessary to administer another 2,500 cc. of blood before his blood pressure stabilized. The bleeding point was never found and hemorrhage recurred.

Comment: The renal hemodynamic response to Aramine in this patient was quite similar to previous observations made on the response to norepinephrine. Following blood pressure elevation, renal blood flow and glomerular filtration rate increased. As the glomerular filtration rate increased, sodium, potassium and water excretion also increased (fig. 2B). The response to Aramine was about the same as the response to the blood transfusion.

The following case represents an example of a relatively poor initial renal hemodynamic response to both norepinephrine and blood transfusions in a patient who was in severe shock from blood loss and trauma.

Case 4. L. M. This 52-year old Negro woman was admitted to the hospital after being hit by an automobile. She was in shock associated with multiple fractured ribs, a left pneumothorax, subcutaneous emphysema, and hemorrhage into the pleural space. The pulse rate was 110 and the blood pressure was 70/30 following the administration of 1,000 cc. of 5 per cent glucose in water. The patient was completely anuric. Therefore, renal blood flow and glomerular filtration rate could not be estimated. Norepinephrine was administered by continuous intravenous infusion and the blood pressure in-



A *B*

FIG. 2. (*A*). Renal hemodynamic response to Aramine and blood transfusion. As the blood pressure increases, glomerular filtration rate and renal blood flow increase. (*B*). Associated with the increase in glomerular filtration rate following Aramine administration, sodium and potassium excretion rates increase sharply. (Patient M. C.)

creased to normotensive ranges. Despite a marked increase in renal blood flow, glomerular filtration rate did not show a parallel improvement. A similar response to blood transfusion was observed. However, 24 hours later the glomerular filtration rate had increased to within normal range with no further therapy. Despite a minimal initial increase in glomerular filtration rate, water and electrolyte excretion increased sharply as the blood pressure was elevated with either blood transfusions or norepinephrine.

Patients in normo-volemic shock (Group II)

Case 5. D. L. This 53-year old white man had had an anterolateral myocardial infarction. His blood pressure on admission was 70/35 (fig. 3). The patient was given norepinephrine by continuous infusion at a rate of 4 micrograms per minute and his blood pressure increased to 98/60. The urine output rose from 0.4 cc. to 1.6 cc. per minute. The glomerular filtration rate increased from 48 cc. per minute to nearly normal. Recovery was uneventful.

Case 6. T. R. This 63-year old white man was admitted to the hospital in shock due to a large anterior myocardial infarction (fig. 4). His systolic blood pressure was 56 mm. Hg. The diastolic pressure was unobtainable. When the blood pressure was increased to 90/75 with norepinephrine, the glomerular filtration increased from approximately 12 cc. per minute to 37 cc. per minute. This was only a partial response since the normal glomerular filtration rate for this man was 110 cc. per minute. He required increasing amounts of norepinephrine in order to maintain the blood pressure, and death occurred 15 hours after therapy was started. There was a progressive deterioration of renal function during this period.

Case 7. L. H. This 29-year old Negro woman was admitted, having produced a criminal abortion three days previously with concentrated Lysol (R). Secondary infection had occurred. She had been oliguric for three days and was in shock on admission. Her blood pressure was 54/8. Her temperature was 102 F. The white blood cell count was 40,000 and the blood urea nitrogen was 38 mg. per 100 cc.

The patient was given 2,000 cc. of 5 per cent glucose in distilled water, and the blood pressure stabilized at 65/50. Control observations on renal function were made. Control urine volume was 0.4 cc. per minute. Norepinephrine was then started and the blood pressure increased to normotensive ranges. Although renal function was markedly depressed prior to norepinephrine administration, as the blood pressure increased glomerular filtration rate showed a three-fold increase and renal blood flow a two-fold increase. The patient was given antibiotics and supportive therapy. After 24 hours it was no longer necessary to administer a vasopressor agent. She showed evidence of increasing azotemia for the next two days, following which urinary function gradually returned toward normal and recovery was uneventful. Her blood urea nitrogen had risen as high as 96 mg. per 100 cc. on one occasion during her illness. Renal function studies repeated

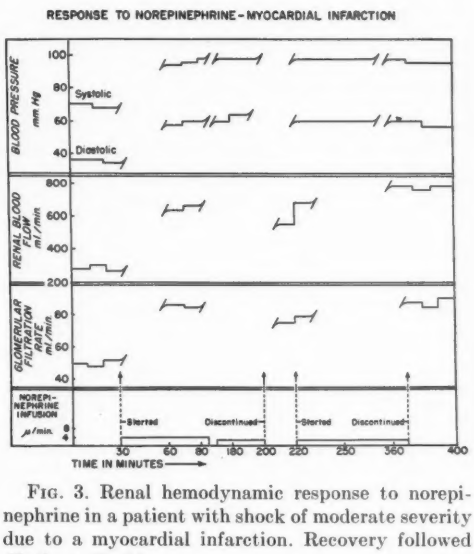


FIG. 3. Renal hemodynamic response to norepinephrine in a patient with shock of moderate severity due to a myocardial infarction. Recovery followed (Patient. D. L).

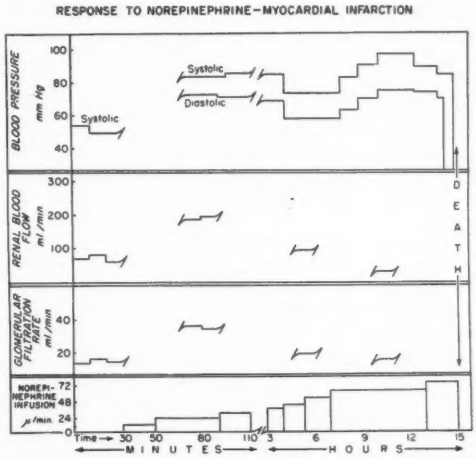
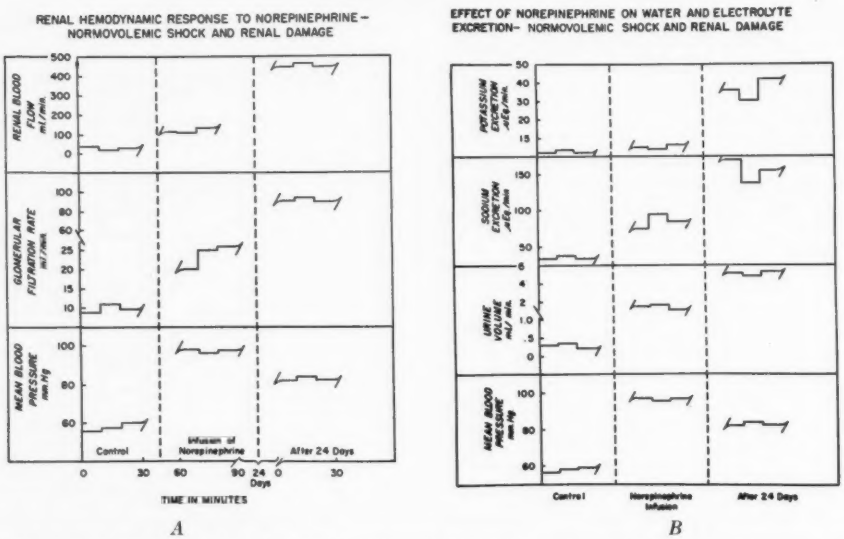


FIG. 4. Renal hemodynamic response in a patient with severe shock due to a myocardial infarction. Improvement in glomerular filtration rate and renal blood flow was only partial. Increasing amounts of the vasopressor agent were required. Death followed after 18 hours. The increased requirement of norepinephrine was associated with progressive deterioration of renal function. (Patient T. R.).


RENAL HEMODYNAMIC RESPONSE TO NOREPINEPHRINE – NORMOVOLEMIC SHOCK AND RENAL DAMAGE
RENAL BLOOD FLOW ml/min.
GLOMERULAR FILTRATION RATE ml/min.
MEAN BLOOD PRESSURE mm Hg
Control
Infusion of Norepinephrine
After 24 Days
TIME IN MINUTES
EFFECT OF NOREPINEPHRINE ON WATER AND ELECTROLYTE EXCRETION– NORMOVOLEMIC SHOCK AND RENAL DAMAGE
POTASSIUM EXCRETION μEq./min.
SODIUM EXCRETION μEq./min.
URINE VOLUME ml/min.
MEAN BLOOD PRESSURE mm Hg
Control
Norepinephrine Infusion
After 24 Days

A *B*

FIG. 5. (*A*). Patient in shock with primary renal damage due to Lysol. Glomerular filtration rate and renal blood flow were markedly depressed. As the vasopressor agent was administered, both glomerular filtration rate and renal blood flow increased. The increase in renal blood flow may well have prevented the development of irreversible renal damage in this instance. (*B*). Despite a persistent depression of glomerular filtration rate in the presence of renal damage, as the blood pressure increased, the moderate increase in glomerular filtration rate was associated with a moderate increase in water and sodium excretion. (Patient L. H.)

after three weeks indicated that glomerular filtration rate had returned to normal and para-aminohippurate clearance (approximate renal plasma flow) was about 50 per cent of normal.

Case 8. G. H. was a 51-year old white woman with pneumonia, cirrhosis of the liver, and renal failure due to chronic pyelonephritis. On admission, the blood urea nitrogen was 175 mg. per 100 cc., the white blood cell count was 28,300 and hemoglobin was 5.8. The patient was hydrated with 2,000 of 5 per cent glucose in distilled water. The blood pressure was 50/24. Despite a glomerular filtration rate of only 5 cc. per minute, the urine volume was 1.4 cc. per minute. As soon as the blood pressure was increased to normotensive ranges with norepinephrine the glomerular filtration rate increased to 11 cc. per minute and the urine output increased to 4 cc. per minute, indicating that improvement in renal function can be expected even in the presence of severe primary renal disease. These observations are considered qualitative and directional only since accurate estimations of renal blood flow cannot be made under these circumstances.

DISCUSSION

Laboratory Observations. There is no doubt that vasopressor agents are renal vasoconstrictors when administered to the normotensive animal in adequate amounts.[6, 7] Furthermore, this renal vasoconstrictor effect can be blocked off with Dibenzyline, a potent adrenergic blocking agent. This is well demonstrated in figure 6. When either Aramine or norepinephrine were administered to this animal, renal blood flow and glomerular filtration rate were reduced. However, if adrenergic blockade was produced with Dibenzyline and then Aramine was administered at four times the rate previously, renal vasoconstriction did not occur. We have made similar observations after unilateral adrenergic blockade of one kidney by the intra-arterial injection of Dibenzyline. Before Dibenzyline was injected into the left renal artery, norepinephrine infusion (intravenous) produced marked vasoconstriction in both kidneys. After the blocking dose of Dibenzyline was injected into the left renal artery, norepinephrine continued to produce vasoconstriction in the contralateral unblocked kidney but had no effect on the blocked side (left).

By contrast to the normotensive animal

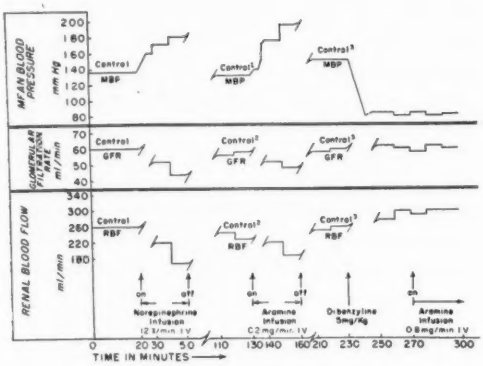


FIG. 6. Renal hemodynamic response to vasopressor agents before and after adrenergic blockade in the dog. (Courtesy American Heart Journal).

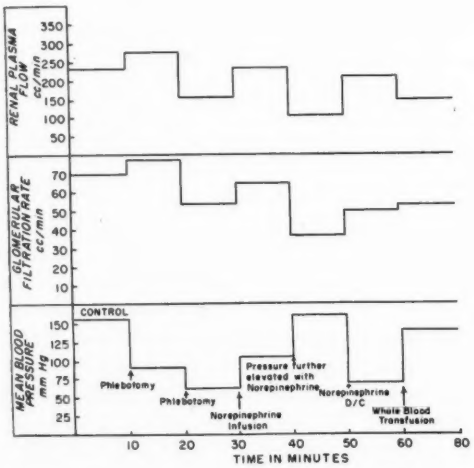


FIG. 7. Renal hemodynamic response to hemorrhage (in a dog) followed by blood pressure elevation with norepinephrine. Renal blood flow was reduced with hemorrhage and increased when the blood pressure was raised with norepinephrine. However, if the pressure was raised to hypertensive levels, renal blood flow and glomerular filtration rate were again depressed.

which is made hypertensive, a different response is observed when vasopressor agents are administered to animals previously made hypotensive by hemorrhage. In the latter animals, renal blood flow and glomerular filtration rate are reduced due to bleeding. When norepinephrine is then administered, renal blood flow and glomerular filtration rate are increased toward the control values although there is usually only partial return (fig. 7).

Clinical Observations. The effect of vasopressor agents on the human kidney in the normotensive subject is quite similar to that observed in the laboratory animal. As the blood pressure increases renal blood flow is first reduced. If the rate of infusion is great enough, glomerular filtration rate may also be reduced (table 5). However, the renal hemodynamic response to vasopressor agents in the presence of shock is entirely different than when these agents are administered to normal subjects. In the shocked patient there exists a marked reduction in renal blood flow and glomerular filtration rate which is due to a combination of renal vasoconstriction and hypotension (tables 2 and 3). When the blood pressure is now increased with a vasopressor agent, some of the renal vasoconstrictor response is relieved and the intraglomerular filtration pressure increases. As a result, renal blood flow, glomerular filtration rate, and urine output are increased.

When glomerular filtration rates before and after treatment with vasopressor agents or blood transfusions are plotted (graphed) against blood pressure in the hemorrhagic shock patients (group I), one can see that the degree of increase in glomerular filtration rate after blood replacement is well interspersed with the response to vasopressor agents, indicating very minor differences, if any, in the overall response. When glomerular filtration rate is plotted against urine volume after blood pressure elevation with either vasopressor

TABLE 5.—*Renal Hemodynamic Response in Control Subjects Made Hypertensive By an Infusion of Norepinephrine (9 Subjects)*

	Control	Norepinephrine	Per Cent of Control Value‡
Mean B.P. (mm.Hg)	97	132	136
GFR (cc/min.)	108	102	94
RPF (cc/min.)	706	417	60
RBF (cc/min.)	1143	705	63
Renal Vascular Resistance	.091	.195	224

‡ Mean for per cent of control value of 9 subjects.
GFR = glomerular filtration rate.
RPF = renal plasma flow.
RBF = renal blood flow.

agents or blood transfusions, one observes that although urine volume increases, the increase in glomerular filtration rate appears to be the primary response. Although the control values for renal function are not considered as quantitative estimations, these observations certainly indicate directional changes following the administration of vasopressor agents and blood since the observations made after blood pressure elevation can be considered more or less accurate because urine volume was quite adequate at this time.

In mild to moderate hemorrhagic shock, blood transfusions do not appear to be superior to vasopressor agents for increasing glomerular filtration rate and renal blood flow (table 2). The increase in blood pressure frequently does not have to be very great in order to produce a rather sharp increase in glomerular filtration rate. If blood loss is too great and very large amounts of norepinephrine are required to raise the blood pressure, improvement in renal function is not observed after the administration of vasopressor agents. However, if part of the normal blood volume is replaced, norepinephrine now produces a significant improvement in renal function (fig. 8). This response

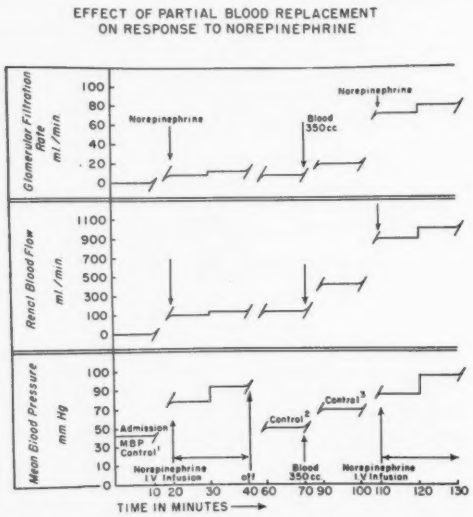


FIG. 8. Renal hemodynamic response to norepinephrine before and after partial replacement of blood in a patient who had suffered a severe hemorrhage.

was observed even though the transfusion was not great enough to have a significant effect on blood pressure.

These responses to vasopressor agents speaks against a humoral agent being responsible for the renal vasoconstriction associated with hemorrhagic shock in man, especially since glomerular filtration rate and renal blood flow return to normal ranges. If a circulating agent were responsible for the renal vasoconstriction which occurs in shock, one would not anticipate that the administration of a second vasoconstrictor would relieve the vascular constriction produced by the first. It is possible, however, but not likely, that norepinephrine directly antagonizes circulating vasoconstrictor substances which are liberated by the patient in shock.

In the patients with normovolemic shock there is a consistent increase in renal blood flow and glomerular filtration rate but they never approach normal ranges. Even though the increase in glomerular filtration rate is not great, there is a rather consistent increase in urine volume and electrolyte excretion.

SUMMARY AND CONCLUSIONS

(1) Renal function studies have been made in patients suffering with clinical shock due to various etiologies. Renal function was determined during shock, during norepinephrine-induced normotension, and in traumatic cases, after blood volume replacement.

(2) Although norepinephrine administration to normotensive human subjects increases renal vascular resistance and depresses renal blood flow, when administered to patients who are in shock the opposite effect results. This ambivalent action of norepinephrine is thought to result from a differential vasoconstriction between the kidney and the remainder of the general circulatory bed. The elevation in blood pressure incident to the administration of norepinephrine to patients in shock is due to an overall increase in peripheral vascular resistance but the lesser renal vasoconstrictor effect results in an increase in renal blood flow and glomerular filtration rate with an actual reduction in renal vascular resistance.

(3) Norepinephrine improves renal function

in all types of clinical shock. In moderate hemorrhagic shock norepinephrine may return renal function to normal. Partial restoration of renal function may be effected with the drug in severe hemorrhagic shock, but complete restoration occurs only if the blood volume is increased towards normal.

(4) It is suggested that norepinephrine is probably useful in protecting the kidneys in cases of hemorrhagic and traumatic shock while awaiting blood volume replacement.

Summario in Interlingua

1. Studios del function renal esseva executate in patientes con choc clinic a varie etiologias. Le function renal esseva determinate durante le choc, durante normotension inducite per norepinephrina, e—in casos traumatic—post reimplaciamento del volumine de sanguine.

2. Ben que le administration de norepinephrina a individuos normotensive augmenta le resistentia vascular renal e reduce le fluxo sanguinee renal, le effecto opposite es observate in casos de choc. Nos opina que iste ambivalentia del effecto de norepinephrina resulta de un differentia del vasoconstriction in le renes e in le resto del circulation general. Le elevation del pression sanguinee effectuate per norepinephrina in casos de choc resulta de un augmento general del resistentia vascular peripheric, sed le reducite effecto de vasoconstriction renal resulta in un augmento del fluxo sanguinee renal e del filtration glomerular con un effective reduction del resistentia vascular renal.

3. Norepinephrina meliora le function renal in omne typos de choc clinic. In casos de moderate choc hemorrhagic, le effecto de norepinephrina pote esser le retorno del function renal al normal. Un restauration partial del function renal pote resultar del uso del droga in casos de choc hemorrhagic sever, sed un complete restauration resulta solmente si le volumine del sanguine es augmentate usque a valores normal.

4. Nos opina que norepinephrina es probabilemente utile in proteger le renes in casos de choc traumatic e hemorrhagic durante le intervallo ante le reimplaciamento del volumine sanguinee.

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The Elimination of Body Resonance Distortion from the Direct-Body Ballistocardiogram

By Michael Tobin, M.E.E., John N. Edson, M.D., Robert Dickes, M.D., Gerald H. Flamm, M.D. and Lawrence Deutsch, B.E.E., M.D.

A simple method of obtaining a force ballistocardiogram has been presented. This type of tracing has been derived from the direct-body ballistocardiogram by electrically filtering out body resonance distortion. The resultant force tracings appear to be closely related to cardiovascular events.

THE recorded ballistocardiogram is a distorted representation of cardiovascular forces.[1, 2, 3] These forces, which are generated by the contracting heart and accelerated blood, are transformed in transmission to the surface of the body. The resultant body movement is determined by the amplitudes of the transmitted forces and the mechanical response of the body. It is the purpose of this paper to present a practical means of neutralizing the distorting effect of the body's resonance on the longitudinal ballistocardiogram of the supine subject lying on a rigid surface.

The longitudinal motion of the supine body may be described mathematically, if it is assumed that the body behaves as a simple mechanical system. The normalized displacement and velocity amplitude responses of such a simplified body to sinusoidal forces are given in equations (1) and (2):[4, 5, 6, 7]

$$(1) \qquad X = \frac{1}{\sqrt{(1 - S^2)^2 + (2rS)^2}}$$

$$(2) \qquad V = \frac{(2rS)}{\sqrt{(1 - S^2)^2 + (2rS)^2}}$$

where r is the ratio of actual damping to the critical damping of the body and S is the ratio of the frequency under consideration to the resonant frequency of the body.

The displacement and velocity of the body are derived in normalized form in order to effect optimum simplification and generalization of equations. Thus, the four parameters, mass, elastance, damping and frequency are replaced by two parameters, normalized damping and normalized frequency. The generalization effected by normalization makes equations (1) and (2) more readily applicable to all subjects.

The amplitude response curves shown in figure 1, plotted from equations (1) and (2), graphically demonstrate the variation of body motion with frequency. This variation of body response with frequency is the basic cause for distortion in the recorded ballistocardiogram.

One method of correcting this distortion consists of analyzing the recorded ballistocardiogram and resynthesizing a new tracing by the Fourrier method.[2] The corrected tracing is free of body resonance distortion. However, this method does not yield a continuous corrected record and is, therefore, unsuitable for clinical ballistocardiography.

A second method of correcting the distortion introduced by the body's resonant response consists of recording the ballistocardiogram by means of specially designed beds. Talbot and his coworkers[8] approximate a tracing free of distortion due to the body, by recording the ballistocardiogram from a board floating in a mercury filled tank. von Wittern[3] records the ballistocardiogram from a pendular bed adjusted so as to mechanically filter the distortions introduced by the body and the bed. Both technics can approximate undistorted ballistocardiograms. However their application

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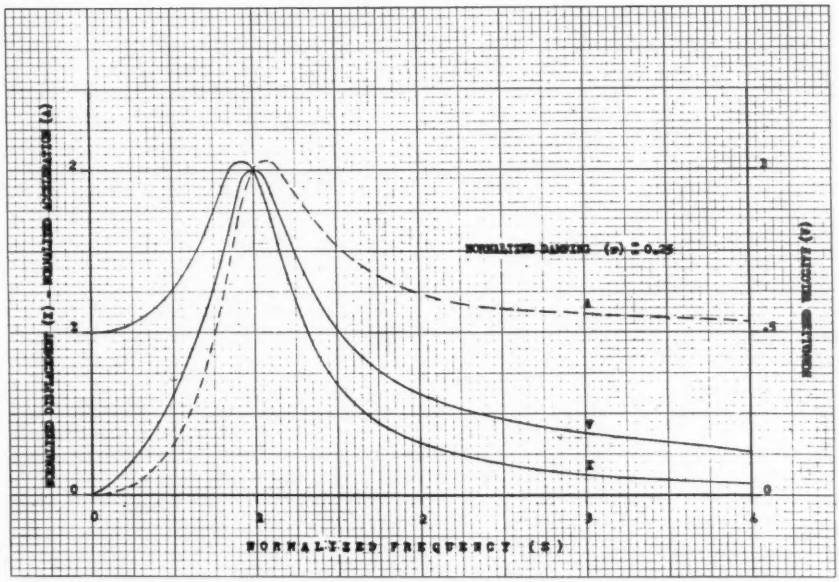

FIG. 1. Normalized displacement, velocity, (and acceleration) amplitudes with respect to normalized frequency at an assumed normalized damping of 0.25, for a simple mechanical system.

$$\left(\text{The acceleration } A = \frac{(S)^2}{\sqrt{(1 - S^2)^2 + (2rS)^2)}}\right)$$

to clinical ballistocardiography is limited by the complexity of the mechanical systems.

A third method of obtaining a distortion free ballistocardiogram is relatively simple and is based on the Dock[9] method of recording directly from a body lying on any rigid structure. This method consists of devising electric filters whose amplitude responses are inverse to the curves shown in figure 1, and whose phase shifts linearize the body phase responses shown in figure 2. The introduction of such a corrective circuit between a transducer and amplifier will produce a flat (undistorted) response. Thus, the recorded ballistocardiogram will be directly proportional to the transmitted cardiovascular forces.

METHOD

The resonant frequency and damping constant of a subject were measured by recording the damped oscillation subsequent to manual displacement of the supine body from its resting position.[2] These constants were then substituted in equations (1) and (2) and the displacement and velocity responses of the body were determined. Finally, electric filters (fig. 3) were designed to correct these re-

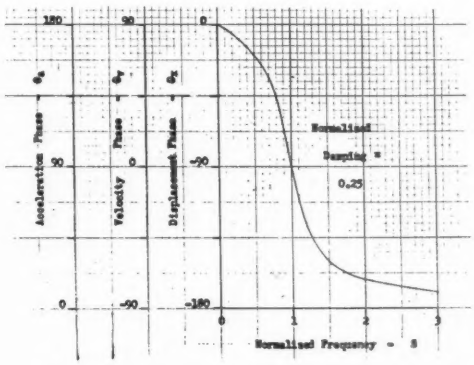

FIG. 2. Displacement, velocity, (and acceleration) phase shifts with respect to normalized frequency at an assumed normalized damping of 0.25, for a simple mechanical system. The equations representing these phase responses are as follows:

$$\theta_x = -\tan^{-1}\left(\frac{2rs}{1 - s^2}\right)$$

$$\theta_v = \theta_x + \frac{\pi}{2}$$

$$(\theta_a = \theta_x + \pi)$$

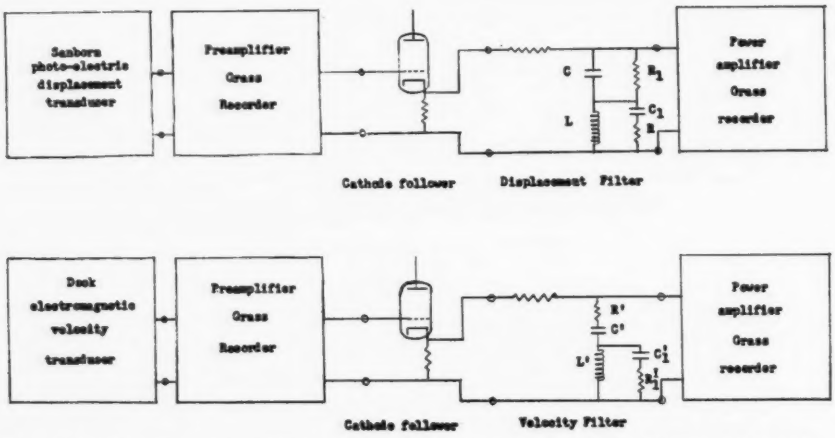

FIG. 3. A schematic representation of the displacement and velocity filters used to eliminate body resonance distortions from the ballistocardiogram; and the placement of these filters in the recording systems.

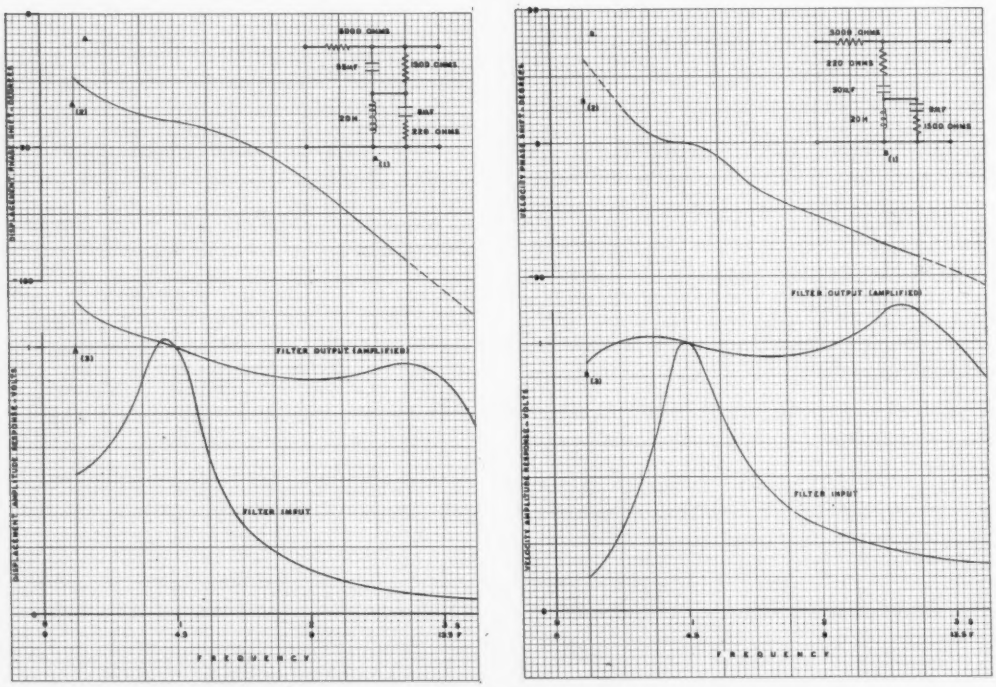

FIG. 4. Responses of displacement and velocity filters used for a subject whose body resonant frequency is 4.5 cycles per second and whose normalized damping is 0.25. $A_{(1)}$ and $B_{(1)}$. Displacement and velocity filter diagrams. The coils (United Transformer Company—N 1181) have a Q of approximately 5, at 5 cycles per second. $A_{(2)}$ and $B_{(2)}$. Displacement and velocity phase shifts of the body-filter systems. $A_{(3)}$ and $B_{(3)}$. Measured displacement and velocity filter input and output voltages as functions of frequency. The filter output voltages are amplified so as to yield 1 volt output at 4.5 cycles for a filter input of 1 volt. Note the linear phase shifts and the flat amplitude responses effected by the filters.

sponses. Variations in body resonant frequency from subject to subject were compensated for by varying the parameter C (or C′). The changes in the damping ratio were corrected by varying R (or R′).

This method of correction was applied to five normal subjects. Simultaneous corrected and standard longitudinal direct-body displacement and velocity ballistocardiograms were recorded from the legs by means of the Sanborn photoelectric displacement transducer and the Dock electromagnetic transducer.[9] Lead I of the electrocardiogram was recorded simultaneously with the ballistocardiograms. Heart sounds and respiration were also included in some tracings. All recordings were obtained with the subjects lying on a concrete floor.

The high impedance of the Sanborn photoelectric transducer (approximately 2 megohms) necessitated its isolation from the relatively low impedance displacement filter (6 to 7 kilohms). The electromagnetic transducer did not need to be isolated from its filter since the impedance of the former is approximately 1 kilohm, whereas the latter is approximately 7 kilohms. However, to assure uniformity of method the velocity transducer was similarly isolated from its filter. It was convenient to place the filters and isolating cathode followers between the preamplifier and power amplifier of the recorder (fig. 3).*

Results

The subject chosen for illustration here had a body resonant frequency of 4.5 cycles per second and a damping ratio of 0.25. The proper circuit values of the displacement and velocity filters to correct the body resonance distortions of the subject are given in figure 4. The measured response characteristics of the filters and their effect on the displacement and velocity responses of the body are also shown in this figure.

Equalized and standard direct-body longitudinal displacement and velocity ballistocardiograms of this subject are shown in figure 5. The corrected ballistocardiograms are similar to each other and show alteration of the characteristic wave form. The H wave is notched at its peak. The notch occurs at the time of the first heart sound. The J wave is bipeaked. The JK stroke is shortened. The L wave is replaced by high frequency oscillations occurring at the time of the second heart sound. The diastolic waves are replaced by high frequency oscillations.

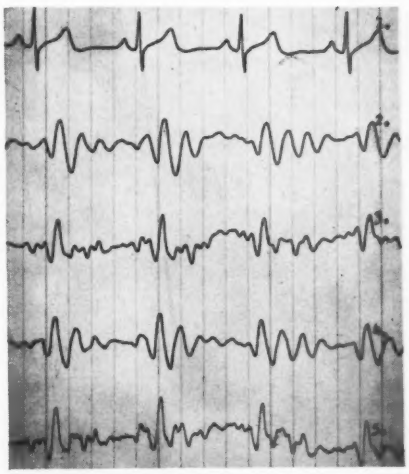

FIG. 5. Standard and corrected displacement and velocity ballistocardiograms recorded from the legs of a supine subject, whose body resonant frequency is 4.5 cycles per second, and whose body damping is 0.25. Simultaneous tracings are: 1. Electrocardiogram lead I. 2. Displacement recording using the Sanborn photoelectric transducer. 3. The displacement response (2) corrected by the displacement filter. 4. Velocity recording using the Dock electromagnetic transducer (without bypass capacitor). 5. The velocity response (4) corrected by the velocity filter.

Discussion

The representation of the body as a simple mechanical oscillator is, of course, an oversimplification. The concept, however, is useful as a working hypothesis, and is supported by the following laboratory data:

(1) The damped oscillation of the supine longitudinal body in response to a manual displacement mimics the oscillatory decay of the simple mechanical oscillator.

(2) Nickerson and Mather[2] find reasonable agreement between the motion of the supine body along the longitudinal axis, when forced by a mechanical generator, and the motion of a simple mechanical oscillator.

(3) The correction of the displacement and velocity ballistocardiograms, by means of filters whose responses are inverse to the theoretical displacements and velocities of the

* Grass 8 Channel Electroencephalograph, Model IIID.

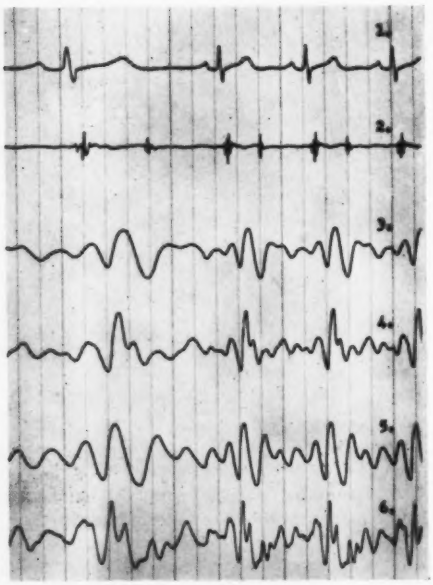

FIG. 6. Standard and corrected, displacement and velocity ballistocardiograms. The recordings were corrected during a change in paper speed from 60 mm. to 30 mm. per second. Note the high frequency phenomena in the corrected tracings (see text). Simultaneous tracings are: 1. Electrocardiogram lead I. 2. Heart sounds recorded from the apex. 3. Displacement recordings using the Sanborn photoelectric transducer. 4. The displacement response (3) corrected by the displacement filter. 5. Velocity recording using the Dock electromagnetic transducer without bypass capacitor. 6. The velocity response (5) corrected by the velocity filter.

simple mechanical oscillator, yield recordings that are similar to each other.

The two corrected recordings can, therefore, be considered approximate tracings of the transmitted cardiovascular forces. Such a force ballistocardiogram could just as readily have been obtained by using an acceleration transducer[10] in combination with a suitable filter. The particular transducer-filter system chosen to record the force ballistocardiogram is a matter of convenience.

The appearance of high frequency oscillations in the corrected ballistocardiograms is due to the equalization of the overall responses effected by the filters. The high frequency oscillations which are normally masked by the accentuated body oscillations at the resonant frequency are presented in more correct proportion by the method of equalization.

Some of the high frequency oscillations are related to cardiovascular events (figs. 5 and 6). Those oscillations in time with the first and second heart sounds are related to the closing of the heart valves.[11] The bipeaking of the J wave is similar to that seen in thoracic ballistocardiograms, and has been attributed to the separate recoils of blood in the pulmonary artery and in the arch of the aorta.[12] The various high frequency oscillations are more prominent in some of the corrected tracings (fig. 6).

The typical force ballistocardiogram presented by Talbot and his associates[8] has a configuration comparable to those shown in figures 5 and 6. In their tracing the H wave is discernibly notched, the J wave shows evidence of a second peak, the JK stroke is shortened, and the L wave and the diastolic waves are replaced by high frequency oscillations.

The force ballistocardiogram presented by von Wittern[3] shows evidence of notching on the H wave, and has a shortened JK stroke. However this ballistocardiogram does not show some of the high frequency markings evident in our tracings and in those presented by Talbot and his colleagues.

Basically our tracings and those presented by Talbot and coworkers and von Wittern are quite similar despite the differences in recording methods.

The floating bed used by Talbot and associates is conceptually simple. The only constraints on the bed are those due to the viscous damping and surface tension of the mercury. As a result the body and bed move almost synchronously and the recorded ballistocardiogram is relatively free of body resonance distortion.

The pendular bed used by von Wittern is more complex. The subject must be clamped to the platform and external damping must be added to mechanically filter the distortion due to the motion of the body with respect to the bed.

The development of a force ballistocardiogram by electric filtering technics is readily applicable to the direct-body ballistocardiograph, but cannot be practically applied to

table ballistocardiographs (such as the Starr[1] or the Nickerson[13] table). The table ballistocardiogram is a function of the body-table system response to cardiovascular forces. The responses of the body and the table cannot be analyzed separately (as proposed by Nickerson and Mather[2]) since the table impedance loads and modifies body activity. The calculation of this loading effect and the design of variable electrical filters to effect an overall correction of table ballistocardiograms suitable for a wide range of subjects is difficult.

The method of obtaining a force ballistocardiogram by electrically filtering the direct-body tracing is simple. This method does not require any special ballistic bed; and the tracing can be recorded with either a displacement, a velocity, or an acceleration transducer. The distortion introduced by the body is easily defined and can be readily corrected by a suitable electric filter.

Summary and Conclusions

A mathematic analysis of body displacement and velocity in response to cardiovascular forces was presented on the assumption that the body behaves as a simple mechanic system.

Guided by this analysis, electric filters were developed to eliminate body resonance distortions from the direct-body displacement and velocity recordings.

The corrected tracings were similar to each other, and it was concluded that they both approximated the force ballistocardiogram.

The corrected ballistocardiograms showed evidence of physiological events, such as heart valve closure, not seen in the standard ballistocardiograms.

Summario in Interlingua

Es presentate un analyse mathematic del displaciamento e del velocitate corporee in responsa a fortias vascular, basate super le postulato que le corpore se comporta como un simple systema mechanic.

De accordo con le datos assi establite, nos ha disveloppate filtros electric pro eliminar distorsiones, resultante del resonantia corporee, ab le directe registrationes de displaciamento e velocitate.

Post le correction del duo registrationes per iste methodo, illos esseva simile le un al altere, e nos concludeva que ambes se approximava al ballistocardiogramma de fortia.

Le corrigite ballistocardiogrammas reflecte certe eventos physiologic—per exemplo le clausion del valvula cardiac—que non es visibile in ballistocardiogrammas standard.

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Interim Report of the Committee on Auscultatory Phenomena of the Scientific Council of the American Heart Association

THE recording on magnetic tape of the sounds produced by the heart and lungs has reached a fairly high degree of perfection as used at several centers throughout the country. It has advantages over other methods, but there are many problems still to be overcome before magnetic tape recordings can be used as universally as electrocardiography, for example.

Instrumentation. The greatest handicap to the general application of tape recording of heart and lung sounds at the present time is that very few instruments are made especially for the recording of these sounds. The vibrations produced by the heart and lungs are low in the auditory spectrum and occur mainly in the range of 40 to 1000 cycles per second. This is well below the average range of both music and the spoken voice and requires that the equipment faithfully record and reproduce in this low frequency range.

Currently, the only available and satisfactory equipment is very expensive. No tape recorder, retailing for less than about five-hundred dollars, has been found to be satisfactory. In addition to the tape recording instrument, a special microphone and some form of loudspeaker or stethophones must be used and this further increases the cost of a satisfactory instrument. All of the component parts of the system must be properly matched and integrated from an electrical standpoint, often with the addition of preamplifiers or power amplifiers. These considerations indicate special difficulties for those without considerable experience in this field.

This Committee is now undertaking a study of the response characteristics of various available instruments. It is hoped that it will soon be possible to set up minimum specifications which must be exceeded by any equipment used for the recording and playback of heart sounds.

It is hoped that in the near future, instruments, designed specifically for this purpose, and at a reasonable price, will become available. Until then, caution is indicated since reproduction of heart sounds is a different problem from the reproduction of music or speech. An instrument may reproduce voice or music satisfactorily and still be totally inadequate for the reproduction of heart sounds.

Tape Speed. This Committee has voted to standardize, for the present, on two speeds: 7½ and 1⅞ inches per second. Because of the low frequencies of the heart sounds and murmurs, fast tape speed is not essential. It is hoped that with the development of appropriate instruments, the use of the slower speed may become generally available. This would provide a considerable saving in tape and the tape loops used for teaching can be shortened. For proper fidelity the tape must always be played back at exactly the same speed at which it is recorded.

Loudspeaker and Stethophone Reproduction. The electrical output of the tape recorder may be put either into a loudspeaker or electronic stethophones. If a loudspeaker is used, it must be an instrument which is adequately designed to handle these low frequencies. The less expensive speakers are unsatisfactory for this purpose. Some degree of sound-conditioning of the room in which the speaker is used is advisable for the most satisfactory results. If desired, the physician may place his own stethoscope in his ears and listen with the bell held toward the speaker. Loudspeakers are advantageous in handling large groups, but there is more difficulty in demonstrating directly from patients due to the "feed back."

Sounds from adjacent rooms may be distracting.

Some physicians prefer the use of individual electronic stethophones whereby the sound is led directly to the ears through earpieces similar to the acoustic stethophone. While this does not require any sound-conditioning of the room and gets around "feed back" and distracting sounds, it does require that an individual electronic stethoscope be available for each person.

Loudspeaker or stethophonic reproduction may be used according to the preference of the individual. The system used should be the one that seems to give the most faithful reproduction under conditions of use.

Reels vs. Loops. Tape may be used either on reels or as continuous loops. In learning auscultation, the continuous loop is more satisfactory since one can listen to any single example for as long, or as short a period as desired before going on to another example. For best reproduction, additional idling and tension pulleys should be available to hold the loops taut. Loops may be of various lengths and there is now no accepted standard length.

If a standard speed and length of loop is adopted, the additional tension pulleys must also be standardized.

Tape Library. As soon as the necessary technical arrangements can be made this committee will set up a tape library under the auspices of the American Heart Association. This library will have facilities for the reproduction of tape recordings of auscultatory phenomena, which will then become available on a purchase basis.

Simultaneous Visualization of the Stethogram. By combining a special type of oscilloscope with the tape recorder, it is possible to visualize the sound (stethogram) at the same time that it is heard. Some teachers feel this audiovisual combination greatly enhances the value of tape recordings.

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CLINICAL PROGRESS

Editor: HERRMAN L. BLUMGART, M.D.

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The Clinical Use of Digitalis Preparations

By CALVIN F. KAY, M.D.

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NOTE: *In view of the length of this article, it will be published in two issues. This issue will contain parts I through IV. The second part, V through IX including the references, will be published in August, 1955.*—ED.

FOXGLOVE, like squill and many other plants now known to possess cardioactive principles, has been used medicinally for centuries. It was in the 18th century, however, when Withering immortalized the old woman of Shropshire in medical history, that the present vast use of digitalis had its beginning. Today, drugs of the digitalis family include those derived from *Digitalis purpurea*, *Digitalis lanata* and certain members of the strophanthus family. They are distributed for oral or parenteral administration under a bewildering number of names. The stock of a large pharmacy ordinarily includes 30 or more oral preparations alone, in tablets or capsules of many sizes, shapes, and colors. The physician who believes he can identify a digitalis preparation from a patient's description may find it disillusioning to inspect an array of these samples.

The cardioactivity of each of these preparations is based upon the content of one or more *glycosides*, each of which has a specific molecular structure.[1, 2] Some of the glycosides are present in the plant and are called natural glycosides. Others are derived from the natural glycosides by the removal of glucose and acetyl groups from the molecule, a procedure which alters relatively little the pharmacologic properties of the glycoside. The further removal of sugar groups (digitoxoses from the digitalis glycosides, rhamnose or cymarose from the strophanthin glycosides) leaves an *aglucone*, which is less potent than its parent glycoside. Each aglucone is a phenanthrene structure to which is attached a lactone ring. The phenanthrene

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structure itself is shared by many biologically important substances: cholesterol, ergosterol, sex and adrenal hormones, and bile acids, for example. The biological characteristics of the phenanthrene derivatives are largely determined by the nature and position of the substituent groups. The lactone ring at position 17 is characteristic of the selective cardiac action of the aglucones from which they are derived.

While the digitalis preparations constitute such a large family that to know the commercial name for every member of it would be a burden on the memory, the physician should be able to distinguish child from grandparent and cousin from brother. The adult working parents of the family are the glycosides. Their parents are the galenical vegetable preparations, of which whole leaf digitalis is an example, and their offspring are the aglucones, degradation products that with one exception are not present among the standard pharmacological preparations.

I. The Various Digitalis Preparations

I. *Digitalis purpurea* in its whole leaf form is the only grandparent in general use. It consists of inert material and biologically active mixed natural glycosides. The biologic assay of digitalis is based upon measurement of the lethal dose in pigeons. So determined, the potency must be not less than 85 per cent nor more than 120 per cent of the potency of U.S.P. Digitalis Reference Standard. One U.S.P. unit is defined as 0.1 Gm. of reference standard. In 1936 the potency of the U.S.P. unit was increased by approximately 30 per cent in order to correspond with the International Standard. The term "cat unit" was formerly used to define the potency of digitalis biologically assayed in cats against a U.S.P. unit. A large number of whole leaf preparations or extracts, standardized in terms of U.S.P. digitalis units, are available under many trade names.

The natural glycosides of *Digitalis purpurea* are not prepared commercially in purified form, but two derivatives are in use:

a. *Digitoxin* is derived from a natural glycoside of *Digitalis purpurea* by the removal of glucose. The aglucone of the pure crystalline substance is digitoxigenin. As commercially distributed, digitoxin U.S.P. is not necessarily pure digitoxin. It is assayed chemically by a procedure that accurately measures its content of cardioactive glycosides. It must have a purity of not less than 95 per cent in comparison with U.S.P. Digitoxin Reference Standard. However, gitoxin is also measured in the chemical assay as though it were digitoxin. Commercial samples of digitoxin U.S.P. have been found to contain varying but appreciable amounts of gitoxin[3] which has relatively little biologic cardioactivity. Thirty-one commercial preparations were recently tested by the pigeon bioassay technique for digitoxin formerly used (U.S.P. XIII and preceding). Three of these did not meet the potency standards then employed. However, two of the three were also inadequate chemically, to a lesser degree.[4] Digitoxin U.S.P. is distributed under several trade names.

b. *Gitalin* (*amorphous*) is a mixture of natural glycosides prepared from *Digitalis purpurea* by a special extraction and purification process. It was formerly known as verodigin, N.F. No legal requirements for standardization have been established, but bioassay by the manufacturer is presumed to give uniformity approximating that of digitalis U.S.P.

II. *Digitalis lanata* is not used in crude form, but it is the parent of several derivatives now in wide use:

a. Digilanid is a purified mixture of three natural glycosides, in the same proportions as in the plant, namely, about 47 per cent lanatoside A, 16 per cent lanatoside B, and 37 per cent lanatoside C.

b. *Lanatoside* A is not used in purified form, but two commercial preparations are derived from this natural glycoside: 1) *Digitoxin*, identical to that prepared from *Digitalis purpurea*, is derived by removal of glucose and acetyl. 2) *Acetyl digitoxin*, is derived by removal of glucose but not of acetyl. Its pharmacologic properties have been recently studied experimentally and clinically,[5, 6, 7] and it is now available commercially.

c. *Lanatoside C*, a purified natural glycoside, is in wide clinical use, especially intravenously for rapid effect. It is a U.S.P. preparation; its

potency, by pigeon bioassay, may legally vary from 85 per cent to 120 per cent of the Lanatoside C Reference Standard. 1) *Digoxin* is pharmacologically similar to lanatoside C and is derived from it by removal of glucose and acetyl groups. Digoxin U.S.P. contains not more than 110 per cent nor less than 90 per cent of the labelled amount, standardized by colorimetric assay comparison with U.S.P. digoxin Reference Standard.

III. *Ouabain* Injection U.S.P. is a natural glycoside obtained from the seeds of *Strophanthus gratus* or from the wood of the ouabao tree. It is assayed against a U.S.P. reference standard in pigeons, with the range 85 to 120 per cent permitted. It is for intravenous use only.

IV. *Strophanthin K* is a mixture of three or more natural glycosides derived from *Strophanthus kombe*. As prepared for intravenous use, it is standardized (N.F. IX) to half the potency, per milligram, of Ouabain U.S.P. *K-Strophanthoside* is a natural glycoside isolated from the mixture. The aglucone of each of the glycosides of strophanthin K and of ouabain is strophanthidin.

a. *Acetyl strophanthidin* is the only preparation now in use that is neither a glycoside nor a mixture of glycosides. It is a synthetic elaboration of the aglucone strophanthidin. It is for intravenous use only. Its biologic effects are the most rapid in onset and the least persistent of any member of the digitalis family of drugs. It is biologically assayed in cat units against a reference standard. Five tenths mg. of the drug is approximately 3 cat-units.

II. The Distribution and Fate of Digitalis

An ingested digitalis preparation, if absorbed, must be distributed in the blood to various tissues, and finally destroyed or excreted. Until recently it has been impossible to study this problem adequately because there were no methods for the detection and measurement of the minute quantities of glycoside necessary to produce major biologic effects upon the heart. Two such technics have been developed. One, developed by Geiling and his associates,[8] is based upon the radioactivity of a biosynthetic digitoxin incorporating C^{14} in the molecule. Minute amounts are detected by radioisotope technics. This method is extremely sensitive and accurate, but unfortunately, it is the C^{14} that is measured, not the digitoxin. Therefore, other means must be used to differentiate the presence of the drug itself from its metabolic degradation products. Also, even in minute doses, C^{14}, with a half-life of 5,600 years, presents an uncertain hazard for experimentation in human subjects, although the amount remaining in the body after a few weeks is almost infinitesimal. The second method, developed by Friedman and Bine[9] as a modification of the chick embryo heart technic of Paff,[10] is based upon the development of arrhythmias in the embryonic duck heart when immersed in media containing cardioactive glycoside. With these two technics, much has been learned of the fate of digitoxin in man and animals. An excellent review of the critical experiments has been written by Friedman.[11]

Investigators using many different technics have agreed that ingested digitoxin is completely absorbed. In varying degree, other glycosides are less potent orally than intravenously. Whether these other drugs are destroyed in, or poorly absorbed from, the gastrointestinal tract is not known. In the plasma, digitoxin is adsorbed on albumin.[12, 2] This probably accounts for the old observation that digitoxin in a plasma perfusate is less rapidly lethal to an experimental preparation than when it is delivered in saline. Digitoxin, bound to the albumin, is less free to traverse capillary and cell membranes. Adsorption does not occur between albumin and most other glucosides.

After oral ingestion, the quantity of digitoxin in the blood has thus far defied detection.[11] Given intravenously, the disappearance of this glycoside from the blood has been measured by both of the technics described above. By bioassay, in normal human subjects, 50 per cent disappears within a few minutes. The subsequent drop is more gradual, with 40 per cent still present at one hour, and 15 per cent after two hours.[13] With the C^{14} digitoxin technic, after one hour only 10 per cent remained in the

blood of patients with heart failure. Lanatoside C disappears much more rapidly than digitoxin,[14] presumably because it is not adsorbed by albumin. Contrary to earlier observations, little glycoside is held in extracellular fluids. The digitoxin content of edema fluids is extremely low, never more than .02 mg. per liter.[15] Mobilization of edema fluid does not mobilize digitalis. The digitalis toxicity that may follow mercurial diuresis is, rather, related to the associated potassium depletion.[16]

In the past, it was believed that the myocardium had a unique affinity for digitalis. This belief is not supported by the results of assay by either technic. In experimental animals, equal or greater concentrations of digitoxin are found in the lungs, livers, and kidneys than in the hearts.[17, 18, 19] It may be washed out of the heart with little difficulty[20] in excised preparations and it disappears from the heart and other organs of the intact animal within a few hours.[18, 19] Possibly the biologic effects of digitalis preparations are achieved at the cell membrane, without penetration of the cell by the glycoside or a biologically active degradation product.[21] Whether or not this is true, digitoxin is detected in the soluble supernatant intracellular parts of emulsified cells, but not in the nuclear and mitochondrial portions.[22]

Digitoxin excretion has been studied by the two technics in experimental animals and in man.[18, 23, 24, 25, 26] Considerable species variation is found by both methods and the observations in animals are not applicable to man. In human studies, the results by the two methods are somewhat conflicting. Although 60 to 80 per cent of the C^{14} given in radioactive digitoxin ultimately appears in the urine, with a large excretion in the first few days, less than 10 per cent is thought to be in digitoxin; the rest is in degradation products.[27] By the bioassay technic, the kidneys excrete, as biologically active digitoxin, 40 to 50 per cent of a single dose over a period of more than two weeks. No more than 5 per cent is excreted in a single day. Cardiac patients excrete the drug equally as well as normal persons, but with a slightly longer initial lag.[25] On maintenance doses, whether 0.1 or 0.2 mg. per day is given, a little less than half the administered dose appears in the urine. In toxicity, urinary excretion may reach 0.1 mg. or more.

Little is known of the urinary excretion of glycosides other than digitoxin, or of the fecal excretion of any of the glycosides in man. There are reasons to believe that the latter is small.[11] If the conclusions from bioassay techniques are correct, indicating a long-persistent urinary excretion of about half of the administered digitoxin, then in vivo destruction of the drug must be relatively small; 0.05 mg. per day has been considered a reasonable estimate.[11] Conversely it has been concluded from radioisotope studies that almost all of the digitoxin is metabolically degraded before excretion. Within one hour after injection into a cat of radioactive digitoxin, 74 per cent of the C^{14} content of the heart is already in the molecules of degradation products.[18] Further investigations will doubtless explain these discrepancies. Whether degradation is large or small, the metabolic steps in the process are obscure.

The results by either technique seem to diverge from clinical observation in some important respects. The peak biological effects of digitoxin in the intact human (about eight hours) are much later than the peak concentration of the drug in the hearts of experimental animals, and in man these biological effects persist long after either digitoxin[19] or C^{14} metabolites of digitoxin[18] have disappeared from the hearts of experimental animals. Resolution of these apparent discrepancies must await further development of our understanding of the exact way in which digitalis produces its effects.

III. The Nature of the Action of Digitalis

A list of all the subjective and objective changes possible when a cardioactive glycoside is given to a patient with congestive failure would fill several pages of small print. Some of these changes (e.g., gynecomastia) are incidental, and some are clinically undesirable in varying degree. Fortunately, the most impressive changes are those that reverse the abnormalities of the congestive failure. Among the most consistent of these are: The ventricular

rate slows, the cardiac output increases, the arteriovenous oxygen difference falls, the peripheral venous and right atrial pressures fall and the pulmonary arterial diastolic pressure falls.[28] These cardiovascular hemodynamic changes are accompanied by variable renal vascular dynamic changes and a striking diuresis of water, sodium, and chloride.[28, 29] Since events in the heart, the peripheral vessels, and in the kidney are intimately interrelated, it has been difficult to differentiate primary from secondary effects of the drug.

The effectiveness of venesection in relief of congestive failure has been attributed to a reduction in venous filling-pressure load upon the heart to a point of greater contraction efficiency, i.e., "moving back" toward the peak of the Starling curve. McMichael and Sharpey-Schafer[30] suggested that digitalis was effective in a similar manner, by a primary action in relaxing peripheral vascular tone. They found that a fall in right atrial pressure preceded an increase in cardiac output in patients with congestive failure given digoxin, and that similar effects were achieved by peripheral trapping of blood with thigh cuffs. Further observations from the same laboratories[31] and by others[32, 33, 34] have failed to support this view. Splanchnic trapping of blood in the normal dog after digitalis administration[35] appears to have no counterpart in human congestive failure.[36]

A primary renal action was long ago suggested by the diuresis that follows digitalis therapy. However, digitalis is not an effective diuretic in the absence of congestive failure[37] or in noncardiac edema states except those associated with excessive adrenal steroids.[38] Elevated renal venous pressure has been shown to decrease urine flow and sodium excretion.[39] Although renal hemodynamic changes are small and inconsistent,[38, 40] it is generally accepted that the diuresis produced by digitalis drugs is secondary to their primary action upon the heart.

Digitalis is effective in increasing the output of the heart in failure.[28, 31, 32, 33, 41] It has no such effect upon the normal heart,[32] or upon the enlarged heart that is not in failure.[34] The increased output is occasionally accomplished by slowing the rate or otherwise increasing the efficiency of the pumping mechanism as a whole. Mainly, the effects are the result of an increase in the contractile force of the heart muscle. How this is accomplished is not clear. Indeed, the fundamental reasons for impaired muscular function in clinical heart failure are obscure. There appears to be no deficit in utilization of oxygen by the failing heart.[32] Neither does the synthesis of adenosine triphosphate (A.T.P.), the essential store of chemical energy, appear to be faulty.[42] Rather, the heart in failure is inefficient in converting an adequate supply of chemical energy (A.T.P.) to the mechanical energy of contraction.[42] Fascinating complexities of molecular construction and activity of the myocardium have been described by Szent-Gyorgyi.[21] In the resting state, according to his views, the long, energy-collecting fibers of actin are held separate from the shorter, energy producing myosin by adenosinetriphosphate. The myosin molecules lie like stiff rows of sausages alongside the actin fibrils. With activation, the actin and the myosin join at every eighth link. With this contact, an enzyme is released from myosin that splits adenosine triphosphate from the actin. The adenosine triphosphate then provides the energy to fold the myosin by releasing the ionic structure that holds the link stiff. With the folding of the myosin, the actin fibrils are passively shortened. This act, multiplied by millions of actomyosin units, results in heart muscle contraction. Relaxation is accomplished in a sequence of comparable complexity. These events are exceedingly sensitive to changes in pH, temperature or ionic concentration. When conditions are not optimum, the effectiveness of myocardial contraction is diminished. Experimentally, digitalis tends to restore normal function under many of the unfavorable conditions. It may be that this is accomplished entirely by altering the membrane permeability for ions;[21] the drug, however, has been shown to influence the behavior of actomyosin *in vitro*, after it has been divorced from cell membranes.[43] Until the basic defects of the contraction mechanism in cardiac failure have been disclosed, the exact role of digitalis in restoring normality

will remain obscure. It has been suggested that digitalis replaces the function of some unknown substance, normally present, that has become deficient or to which the muscle has become refractory.[21]

In addition to its influence upon the contractility of heart muscle, digitalis has important effects upon its other physiologic properties: excitability, automaticity, conductivity, and the refractory period. These effects are responsible for the therapeutic value of the drug in the control of ventricular rate in atrial fibrillation and flutter, and in the conversion of one arrhythmia to another or to sinus rhythm. They are also responsible for many undesirable disorders of cardiac mechanism. The problem has been investigated extensively in animals by Mendez and Mendez,[44] Moe and Mendez,[45] Farah and Loomis,[46] Woske and his associates,[47] and many others. From these studies it is apparent that the results are variable from species to species, that the properties of atrial muscle, conduction system, and ventricular muscle are diversely influenced by digitalis, that a given response may be reversed as dosage increases or if the nerve supply is disturbed, and that a change in cardiac mechanism is a net result of complex changes in several properties. In man, we can observe only the net result. The changes in individual physiologic properties can be reconstructed in terms of animal experimental results to only a limited degree.

Moe and Mendez[45] discuss the factors involved in the ventricular arrhythmias induced by digitalis preparations. They are not a product of *irritability*, as the term is commonly used. In the dog, and presumably in man also, irritability (excitability), defined as the responsiveness to stimulation, declines as ventricular arrhythmias increase with higher drug levels. Rather, they are the result of increasing *automaticity* and decreased conduction *velocity*. Ectopic foci produce premature beats. Multiple ectopic foci, isolated from each other by conduction delay, result in progressive chaos terminating in ventricular fibrillation.

Digitalis may produce prolongation of the P-R interval. This is the result of delay in conduction velocity in the A-V conduction system. Atrioventricular block may be attributed either to a decline in intensity of the delayed stimulus to a level below the threshold required to stimulate the ventricle, or to a rise in that threshold as ventricular irritability declines. An increase in refractory period of the A-V node is the predominant factor in the control of ventricular rate with digitalis in atrial fibrillation. The effects of small doses of digitalis upon A-V conduction are caused by vagal stimulation and may be reduced or abolished by denervation, atropine, or exercise. At higher dosage levels, these effects are not reversed by interference with the vagal supply, and are the result of direct action of the drug upon the myocardium.[48]

Digitalis affects all of the physiologic properties of the sinus node and atrium directly, and indirectly, through vagal stimulation. The basis for the conversion of paroxysmal atrial tachycardia to sinus rhythm, or for the conversion of atrial flutter to fibrillation by the drug, is conjectural.

The Relation of Digitalis Action to Cations

The serum concentrations of various cations, especially sodium and potassium, may be altered very little in congestive failure.[49] Conversely, the total body cations content and its intracellular and extracellular distribution are usually disturbed. These changes have an important indirect bearing upon heart function, especially as they relate to blood volume, venous pressure, and fluid accumulation. Unless the disturbances are unusually severe, they have little or no *direct* effect upon the contractile properties of the myocardium, nor do they *directly* induce disturbances in rhythm. They have a critical bearing upon the use of digitalis because the toxicity of the drug may be severely augmented without a parallel increase in its therapeutic properties.

The relationships of heart failure, potassium, and digitalis are discussed in some detail by Lown and Levine.[16] Some potassium deficit, not necessarily associated with a low serum level, commonly occurs in congestive failure. Anoxia, acidosis, or inadequate nutrition may

be contributing factors. This potassium deficiency is made greater by many therapeutic procedures, for example, by dietary restrictions and the use of mercurial diuretics, ammonium chloride, resins or Diamox. Impaired renal function, diabetes, or the use of cortisone may further contribute. It has been shown that the dosage of a digitalis preparation sufficient to produce toxicity is appreciably reduced in the presence of potassium depletion, and that the duration of the toxicity is extended.[16] Also, toxicity develops as potassium is withdrawn by hemodialysis.[16, 50] Digitalis toxicity may be abolished in man[51] and in animals[16] by the administration of potassium even when the blood level is not depressed. High levels of serum potassium have profound effects upon the heart, but their influence upon the therapeutic action of digitalis in man has not been demonstrated. In animals, excessive doses of acetyl strophanthidin were required to produce toxicity when potassium levels had been elevated by hemodialysis.[52]

Sodium deficiency or excess has no such clearly defined influence upon the behavior of digitalis. Calcium and digitalis are synergistic in their propensity to produce an excessive duration of muscle contraction (contracture). Several sudden fatalities have resulted from the intravenous administration of calcium to digitalized patients.[53]

Quantitative Differences in Cardioactive Drugs

The qualitative biologic effects of the cardioactive glycosides are very similar. Indeed, many consider them to be essentially identical in all major characteristics. Some observers, especially in Europe, believe that strophanthus derivatives exert a relatively greater influence upon myocardial contractility and a lesser effect upon junctional tissue conductivity as compared with digitalis and its derivatives. Others assert that preparations vary in the "margin of safety" between the effective therapeutic dose and that which causes toxic manifestations. Although such qualitative differences remain controversial, quantitative differences are very obvious, especially in the percentage of drug absorbed from the gastrointestinal tract, in the rate of measurable onset and cumulation of biologic effects, and in the duration of the effects.

Strophanthus preparations are either destroyed or so poorly and irregularly absorbed from the gastrointestinal tract that enormous doses by mouth are required to produce any appreciable effect, and the therapeutic results are erratic. These drugs should never be used orally. Conversely, digitoxin given orally is completely absorbed within a few hours; hence the effects of a given dose after oral administration are somewhat delayed, but ultimately the same as those to be expected when the drug is given intravenously. Other preparations are incompletely absorbed, as determined by the relative oral and intravenous dosages required to produce an equivalent effect. So determined, about 10 per cent of lanatoside C, 20 per cent of the whole leaf digitalis preparations and 50 per cent of digoxin are absorbed from the gastrointestinal tract,[54] and about 67 per cent of acetyl digitoxin.[5] Incomplete absorption is evidently responsible for the differences between oral and intravenous dosage requirements of all of these other preparations. If absorption were highly erratic between different individuals, the difficulty of reasonable prediction of dosage requirements would be increased. If the degree of absorption were highly variable in the same individual at different times, stable maintenance would be impossible. Fortunately, neither of these problems appears to be of major importance in clinical practice (except, perhaps, in the oral use of lanatoside C).[55, 56] This is attested to by the long and successful treatment record of oral digitalis leaf preparations.

The various cardioactive glycosides influence the heart at variable speeds. Whether the race for biologic effect is measured in an excised turtle heart, a dog heart-lung preparation, or in an intact human subject, the relative order of the drugs remain the same: digitoxin is the slowest, acetyl strophanthidin the most rapid, and the others are in between. The reasons for these differences are not clear. Digitoxin may well be delayed in transit to the heart muscle because it is bound to plasma

albumin. Variation must also exist in the rate at which an effect is produced, once the active principle is present at the cell. Acetyl strophanthidin, for example, is much more rapid in action than lanatoside C despite the fact that, as far as is known, neither is appreciably adsorbed by proteins. Perhaps a "selective cardiac affinity" does exist for some glycosides, although it has not been demonstrated for digitoxin, as noted above.

The development of progressive degrees of biologic effects resulting from the administration of a single dose of different cardioactive preparations is plotted against time in figure 1, with intact man the experimental subject. The curves are derived from a large number of investigations.[5, 16, 56, 57, 58, 59, 60, 61, 62] They are, at best, rough approximations because the responses of different individuals are not uniform; indeed, the preparations themselves are not completely uniform in composition or potency. The terms slight, considerable, submaximal and maximal are deliberately vague. One does not get a "half-maximal" response with half of a "full therapeutic dose." A "half-dose" may reduce the rate in atrial fibrillation from 160 to 85, whereas the "full dose" may reduce it, in the same patient, from 160 to 75. Another patient may show little or no benefit from a "half dose," but a very striking response from a "full dose." It is this very ill-definition of the "level of digitalization" that has made clinical and experimental comparisons between the various digitalis preparations so difficult to evaluate.

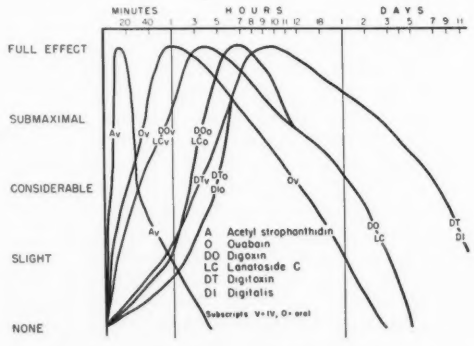

FIG. 1. Approximate curves of accumulation and decline of the biological effects of single doses of cardioactive preparations in man. The curves of orally administered gitalin (amorphous) and of acetyl digitoxin, if plotted, would fall between those of oral digoxin and of oral digitoxin.

The upward curves have several connotations bearing upon the clinical use of digitalis preparations. Among these, two are of special importance. One pertains to the selection of a suitable drug. On the rare occasions when the safety of slower administration must be sacrificed to meet an urgent demand for rapid action, a preparation with a rapidly rising curve is indicated. The other pertains to the time that should elapse between doses of a drug. If further medication is given before the full effects of the preceding dose have accumulated, toxicity is invited.

The biological effects upon the heart of the different preparations wane and disappear at variable rates, as has been abundantly demonstrated by many observations in man and animals. The reasons for the differences are obscure. Little enough is known of the distribution, degradation, and excretion of digitoxin; practically nothing is known by direct measurement of these functions of the other glycosides. The comparative order is the same as for the development of effects, with digitoxin the most persistent and acetyl strophanthidin the most transient. The decline curves of figure 1 vary even more from individual to individual than do the upward curves. They are of special clinical significance with respect to maintenance requirements, duration of toxicity, and re-digitalization. A preparation with a very rapid decline curve is not suitable for long term use because adequate stability of digitalization level is impossible to achieve. A rapid decline curve correlates with relatively large daily maintenance requirements and a relatively short duration of toxicity, if it occurs. When digitalization has been achieved, and then allowed to lapse, the amount of any preparation required to re-establish digitalization will vary in accordance with the glycoside originally used and the time elapsed since its administration. The decline curves provide some indication of the probable requirements.

(*To be concluded in the August issue*)

CLINICAL CONFERENCE

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A Diagnostic Problem: Noncyanotic Heart Disease with Heart Failure in a Seven Year-Old Boy

A Clinical Pathological Conference held at the University of Kansas Medical Center

The Clinicopathological Conference at this school is somewhat unique. Fourth year students are responsible for the discussion of the case, interpretation of x-ray films, and of electrocardiograms. The comments of the students, in the following presentation, reflect the maturity of the modern-day senior.

CASE PRESENTATION

DR. MAHLON DELP, Moderator: Dr. Weber will you present the history of the case which is to be considered today?

Dr. Weber (Senior Resident in Medicine): This 7 year old boy was admitted to the University of Kansas Medical Center on Nov. 25, 1953 for possible surgery, with the chief complaint of "heart disease".

Review of the patients medical history disclosed that at the time of his birth, his parents had been informed that he had an enlarged heart. Cyanosis, however, had not been observed to be present either at the time of birth or later. Squatting behavior had never been noticed. Although the parents had observed that the boy had dyspnea on exertion, his physical development had been normal. Until one month before admission to the hospital, the child had attended school and played well with other children. At that time, however, the patient developed an upper respiratory infection. Dyspnea and easy fatigability had been progressive since this illness. At the time of admission he was unable to walk 10 steps without severe dyspnea. Further questioning disclosed that since birth the patient had numerous respiratory infections and that within the three years just prior to his admission to the hospital he had experienced three illnesses diagnosed as pneumonia. Inguinal herniorrhaphies had been performed in 1949 and 1951.

The family history was essentially negative. The patient's mother did not remember any illnesses occurring during pregnancy. There were no siblings.

On physical examination the patient was observed to appear chronically ill and to be in moderate respiratory distress at rest, but he was not cyanotic. A marked pigeon-breast deformity of the chest and slight kyphosis of the dorsal spine were present. The patient's temperature was 97 F., his pulse rate 124 beats per minute, his respiratory rate 36 per minute, and his blood pressure 90/60. His height was 46 inches and his weight 53 pounds. Veins of the neck were distended and pulsating. The anterior posterior diameter of the chest was increased. The chest was hyperresonant to percussion. The breath sounds were slightly diminished and only an occasional rale was present in the bases. The point of maximal impulse was located in the sixth intercostal space in the midaxillary line. There was a bounding precordial pulsation. A grade II systolic thrill was felt at the apex of the heart. A grade IV systolic murmur was heard along the left sternal border and at the cardiac apex. A grade III diastolic murmur was heard at the pulmonic area. The second pulmonic sound was accentuated. The liver extended 10 cm. below the right costal margin and the splenic tip was palpated at the left costal margin. Pedal edema was not present and pulsations in peripheral arteries were normal.

Urinalysis revealed specific gravity of 1.015; it was otherwise negative. Hemoglobin was 11.1 Gm. per 100 cc. and white blood count was 8,400 with 66 per cent neutrophils. Serology was negative. Nonprotein nitrogen 46.3 mg. per 100 cc., creatinine 1.7 mg. per 100 cc. Serum electrolytes were as follows: Sodium 141 mEq. per liter, potassium 5.7 mEq., chloride 112 mEq., carbon dioxode 27.0 mEq/L. Sedimentation rate was 3 mm. in 1 hour, and the hematocrit 41.5 cc.

In the hospital, the patient received 0.45 mg. of

digitoxin in three divided doses on the first hospital day and thereafter received 0.05 mg. daily. After four days, the child weighed 43 pounds (a 10 pound weight loss) and maintained this weight thereafter. The tachypnea and tachycardia disappeared and the liver-edge receded to a position 2 cm. below the right costal margin.

On Dec. 3, 1953, cardiac catheterization was performed without difficulty. The oxygen saturation values obtained were as follows: Superior vena cava 68 per cent, inferior vena cava 75.5 per cent, right atrium 94.1 per cent, right ventricle 94.1 per cent, right pulmonary artery 94.1 per cent, left pulmonary artery 95.4 per cent. The oxygen saturation in the femoral artery was 96.7 per cent. The mean wedge pressure was 11 mm. Hg, the pulmonary artery pressure was 42/20, the right ventricular pressure was 44/10, and the mean right atrial pressure was 5 mm. Hg.

On Dec. 10, 1953, surgical treatment was attempted with the patient in a state of hypothermia. The patient was given 25 mg. of Benadryl and 1/200 Gm. scopolamine, preoperatively. Anectine (30 mg.) was given intravenously and an endotracheal tube was inserted. At 8:30 a.m. ice was applied; the patient's temperature at this time was 37 C. At 9:15 a.m. his temperature having dropped was 30 C. and the ice was removed. At this time cardiac arrest occurred. Thoracotomy was accomplished rapidly and cardiac massage was started. The patient's body temperature continued to fall and at 10:10 a.m. was 24 C. This was the lowest recorded reading. At 9:45 a.m. a heating pad was applied to the body. An electrocardiogram made at 9:30 a.m. showed ventricular fibrillation. Potassium chloride and later Pronestyl were given into the chamber of the left ventricle without benefit. The electrical defibrillator was used periodically without success. Calcium chloride was later given intracardially, but no improvement in the patient's condition occurred. After cardiac massage had been carried out for a period in excess of two hours without restoration of cardiac action, manipulation was discontinued.

Dr. Mahlon Delp, Moderator: Mr. Tucker, will you present your interpretation of the x-ray films?

Mr. Tucker, Fourth Year Student: The plates showed a large heart with right hypertrophy, particularly obvious on lateral view, and a prominent pulmonary outflow tract.

Dr. Delp: Dr. Tice, do you have any additional comments? Perhaps your fluoroscopic findings would be pertinent.

Dr. Galen Tice, Professor of Radiology: Fluoroscopy showed forceful pulsation in the hilar areas on both sides. The combination of a large right heart and forceful hilar pulsation would make me think first of interatrial septal defect. One might, of course, consider patent ductus arteriosus and mitral valvular disease. The latter could be seriously considered if there were displacement of the esophagus. We cannot ignore the excessive hilar activity noted in this patient.

Dr. Delp: Mr. Van Antwerp, may we have your interpretation of the electrocardiogram as well as the catheter pressure readings?

Mr. Van Antwerp, Fourth Year Student: The electrocardiogram showed a heart rate of approximately 125 beats per minute with regular rhythm. The rhythm arose in the sinus node and conduction between atria and ventricles was prolonged (0.2 second). The P waves were large and peaked, suggesting atrial hypertrophy. The QRS complexes were widened (0.12 second) with a delay in depolarization over the right ventricle. I consider this record indicated right ventricular hypertrophy and atrial hypertrophy.

The pressures were recorded by catheterization in the pulmonary capillary (wedge), left and right pulmonary arteries and right ventricle. The following positive interpretations can be made: (1) No pressure gradient existed between the pulmonary artery and the right ventricle; therefore no pulmonary stenosis was present. (2) Slight pulmonary hypertension was present. (3) The "wedge" pressure was not abnormal. (4) The diastolic pressure was elevated in the right ventricle, a finding compatible with right heart failure.

Dr. Delp: Dr. Dimond, do you have any additional comments about these tracings?

Dr. E. Grey Dimond, Professor of Medicine: No.

Dr. Delp: May I suggest these features of the case in a brief summary. This patient had first been recognized at birth as having heart disease. The clearly described murmurs and especially the diastolic murmur deserve careful consideration. Additional information which may be gathered from the electrocardiogram and pressure readings I leave to you. Hypothermia was utilized in preparation for surgery here but this we wish discussed after the differential diagnosis.

Mr. Miller, we want you to discuss the

differential diagnosis based upon the history, physical findings, and any additional information you gather from pertinent laboratory values. Dr. Dimond will continue the diagnostic discussion. We wish Dr. Reissmann to confine his remarks to hypothermia, its indications, how it is done, and the dangers involved. Dr. Hardin will present his proposed plan of surgery in this case. First, Mr. Miller.

Differential Diagnosis

Mr. Miller, Fourth Year Student: The case today is that of a seven year-old boy who, at birth, was found to have an enlarged heart. This finding raises the possibility of congenital heart disease.

The subsequent developments of dyspnea on exertion, frequent upper respiratory infection and three episodes of illness diagnosed as pneumonia serve only to strengthen this suspicion. The possibility of rheumatic heart disease cannot be ruled out by history, but subsequent developments would tend to point towards congenital heart disease as this patient's main problem. The lack of development of cyanosis through these various infections, plus the clinical picture on admission establish that this child had acyanotic or, at most, potentially cyanotic heart disease.

Displacement of the apical beat to the left mid-axillary line plus x-ray and electrocardiographic findings indicate right atrial and ventricular enlargement. Tachycardia, tachypnea, venous distention, hepatomegaly and cardiomegaly, plus the subsidence of these findings on digitoxin therapy, indicate that this patient was in right heart failure.

The auscultatory finding of systolic murmur actually does not localize the lesion; however, the existence of increased pulmonic second sound, plus fluoroscopic evidence of increased bronchovascular markings and prominent pulmonary conus indicate the existence of pulmonary hypertension.

Thus far, I am able to limit this lesion to one which may cause right heart enlargement and failure without producing these findings on the left side. Common lesions which could give the picture presented are: (1) patent ductus arteriosus, (2) pulmonary stenosis, (3) interventricular septal defect, (4) interatrial septal defect, and (5) Lutembacher's syndrome.

Cardiac catheterization was utilized in this patient, and normal oxygen saturation values were obtained in the superior and inferior vena cava. However, on entering the right atrium, there was found a substantial increase in this value. Thus, in this compartment, there must be mixing of arterial blood with that from the venae cavae. The most common condition which may produce this finding is atrial septal defect.

Another condition which may cause increased oxygen saturation values is anomalous pulmonary venous drainage into the right atrium. This condition can give the exact findings of atrial septal defect, but can only be proved by passing the catheter into this vein.

Other exceedingly rare conditions which are all eliminated as possibilities because of physical and catheterization findings are: (1) persistent atrioventricular canal, (2) atrioventricular fistula between a coronary artery and coronary sinus, (3) tricuspid insufficiency with interventricular septal defect and (4) patent ductus with pulmonary and tricuspid insufficiency.

Atrial septal defect does cause pulmonary hypertension, right heart enlargement, right heart failure, and can give all of the clinical as well as the catheterization findings. Thus, I feel that this patient did have interatrial septal defect.

This condition is notorious for having associated with it other lesions, congenital or acquired. Abbott describes 373 cases of interatrial septal defect, and out of this group, only 73 were uncomplicated. Interventricular septal defect may accompany this lesion, but, in the case being considered here, there was no increase in oxygen saturation value in the right ventricle over that of the right atrium. The existence of pulmonary stenosis is also disproved in this case due to the finding of pulmonary hypertension. While there is an increased oxygen saturation of 1.3 per cent in the left pulmonary artery over that of the right ventricle, which would bring up the possibility of a patent ductus, I believe this difference is probably due to laboratory error. The lack of

typical machinery-like murmur and widened systemic pulse pressure also makes this unlikely.

Mitral stenosis may accompany an interatrial septal defect, this condition being called Lutembacher's syndrome. By history, this patient had an enlarged heart at birth, a finding uncommon in uncomplicated atrial septal defect. With Lutembacher's syndrome cardiac enlargement is the usual finding. The murmur of mitral stenosis although commonly present, has not been observed in a large number of these cases; in the case under discussion it was not heard. Left atrial enlargement is not always present in this condition, and again in this case evidence of such enlargement was absent. There is one finding which does not agree with this diagnosis, and this is the lack of evidence of a greatly enlarged pulmonary artery; however, the roentgenographic findings indicated some enlargement of that artery, and I feel that the diagnosis of Lutembacher's syndrome best explains this patient's illness.

Dr. E. Grey Dimond, Professor of Medicine: Our preoperative diagnosis was interatrial septal defect with or without anomalous pulmonary veins. We arrived at this diagnosis in the following manner:

From history alone we could classify the problem as one of congenital heart disease, acyanotic type. The very loud pulmonary second sound, the diastolic blowing murmur of pulmonary insufficiency, the heavy motile pulmonary artery shadows by fluoroscopy, the electrocardiographic evidence of atrial and right ventricular hypertrophy, all were points indicating this to be a lesion overloading the right heart and pulmonary circulation. This narrowed the field to atrial septal defect, anomalous pulmonary veins, Lutembacher's syndrome, perhaps patent ductus arteriosus or ventricular septal defect.

Realizing that a patent ductus but rarely may be present without the typical murmur, we felt justified in eliminating this as a possibility.

We could not eliminate ventricular septal defect completely without catheterization, although the usual course of a patient with a ventricular septal defect is certainly not one of right heart failure at the age of seven. We have, in the past, seen a two year-old boy with similar findings in whom a large, high, ventricular septal defect was found. However, this is rare and we rather confidently disregarded that possibility in the present case.

Lutembacher's syndrome (interatrial septal defect and mitral stenosis) could not be completely discounted, but we were unable to hear any apical diastolic murmur. Actually, even if we had heard an apical diastolic murmur, I believe I would have simply assumed that the murmur was due to altered flow through the left heart and not due to a mitral stenosis. Repeatedly, our group as well as others, has made the diagnosis of Lutembacher's syndrome, based on the usual findings of atrial septal defect plus an apical diastolic murmur, only to be embarrassed to find a normal mitral valve at surgery or autopsy.

We have previously seen a young child with actively pulsating pulmonary vessels, right ventricular hypertrophy, and right heart failure, who was found at autopsy not to have congenital heart disease, but severe, primary pulmonary endarteritis. The right heart catheterization was done in the present patient primarily to eliminate this condition.

The data obtained at catheterization effectively proved a left to right shunt at the atrial level. We were not successful in threading the catheter into an anomalous pulmonary vein, so we sent the child to surgery with the diagnosis of interatrial septal defect with or without anomalous pulmonary veins.

Although seven is a somewhat older age for subendocardial fibroelastosis, we have seen heart failure in a child of nine with this diagnosis and, therefore, further qualified our preoperative diagnosis by adding to the above: with or without subendocardial fibroelastosis.

Dr. Kurt Reissmann, Associate Professor of Medicine: If one wants to open the right heart in order to repair a septal defect, one has to block the blood flow through the chambers of the heart by occluding the venous inflow. Two methods have been proposed to achieve such a bloodless heart and yet to prevent anoxic tissue damage:

(1) An extra corporeal heart-lung device

that permits the by-pass of the patient's heart and lungs and maintains systemic flow. This can be realized either as a mechanical pump and oxygenator or as a human donor whose circulation is connected with that of the patient.

(2) Hypothermia. The application of hypothermia is based upon the reduction of tissue metabolism and oxygen requirements at lowered body temperature. At a body temperature of 27 C., for example, one can completely occlude the cerebral circulation in a dog for 15 minutes and no demonstrable brain damage will result.

Hypothermia is induced by placing the anesthetised patient in crushed ice or cold water, or by means of a special blanket through which a cooling solution circulates. Anesthesia should be sufficiently deep to prevent shivering which is accompanied by an increase in oxygen consumption and delays the lowering of the body temperature. The desired temperature depends on the type of surgery to be performed. In the case of an open repair of a septal defect, a body temperature of 28 C. is said to give the surgeon up to 10 minutes time to perform his task. The complicating and limiting factor in the application of hypothermia in cardiac surgery is the behaviour of the heart and its tendency to undergo ventricular fibrillation or cardiac arrest.

Our group has studied recently close to 100 dogs in hypothermia, and we were impressed by the unpredictability of the temperature level at which cardiac complications occurred. Some animals fibrillated at 26 C.; others, under the same conditions, tolerated 18 C. The tendency to fibrillate was greatly enhanced when the heart was manipulated. In our experience, electrical defibrillation was much less successful in the hypothermic animal than in the normothermic, which makes fibrillation in hypothermia a particularly serious complication.

The failure of the heart in hypothermia is probably not a simple matter of hypoxia or myocardial ischemia, because no oxygen debt could be demonstrated by measurement of the coronary arteriovenous oxygen difference and lactate or pyruvate level. The energy yielding enzymatic processes are slowed in hypothermia, but they are still adequate for tissues upon which no demands for work are placed during the cold state. The heart, however, continues to work. Even the idling heart, that is, the beating heart that ejects no blood, has a considerable energy expenditure. The characteristic lengthening of the active phase, which at 25 C. occupies as much as 70 per cent of the cardiac cycle, indicates that in the cold state, the energy for systolic contraction is not available instantaneously but only within a prolonged period of time. When the heart's temperature is lowered further, the energy yielding reactions are slowed to such an extent that sufficient energy is no longer available for a coordinated cardiac contraction and the heart will fail in spite of adequate blood and oxygen supply.

From the foregoing, it is understandable that, so far, all attempts to prevent cardiac arrhythmia in hypothermia by means of drugs or various electrolyte solutions have met with little success. In the patient under discussion, ventricular fibrillation occurred at the relative high body temperature of 29 C. I think it likely that the considerable dilatation and hypertrophy of the heart in this case contributed to the early occurrence of fibrillation.

Dr. Creighton Hardin, Assistant Professor of Surgery: Although this discussion is limited to our plan of repair of an atrial septal defect under hypothermia, I think brief mention should be made of methods use of which has led to a successful repair of atrial defect. One may divide them into indirect or relatively blind procedures and the direct, dry-field intracardiac methods.

Gross has utilitized a rubber or plastic "well" sutured to the side of the dilated right atrium. An incision is made within the portion of the atrium contained within the core of the "well." Cohn, Murray, and Bailey use a method of repair of atrioseptopexy. The atrial wall is invaginated and sutured to the atrial septum.

The surgeon is desirous of having an open, dry field in which to work so that any septal repair may be done under direct vision. The pump-oxygenator of Gibbon and the use of

hypothermia are current methods by which this latter procedure may be undertaken.

In using hypothermia the surgeon is relying on general body cooling of the vital organ systems to prevent irreversible anoxia. Occlusion of the venae cavae provides a dry field for the surgeon. Even so the surgeon works against the clock but he has the advantage of visualizing directly the operative field.

The repair of the actual defect, if small and centrally located, can be readily done by simple direct suture. Larger defects precluding the above repair necessitate the use of homologous or autogenous tissue or a plastic prosthesis, atrial appendage, either a free or pedicle graft, vein, or pericardium which will heal over in about 10 weeks. Polyethylene, nylon, polyvinyl sponge are rapidly endothelialized by the sixth week.

The surgical advantages of open cardiac surgery for complete visualization, accurate placement of the sutures and placement of tissue or plastic for the larger defects are obvious.

Contraindications for the surgical repair of atrial septal defects are high pulmonary vascular resistance and beginning reversal of blood flow through the septal defect.

There are many problems of hypothermia which require further study. They have been presented by Dr. Reissmann. Until certain of these problems have been satisfactorily answered through further laboratory studies now in progress, we are not using hypothermia again clinically.

We should mention, however, that successful repairs of atrial septal defects have been reported by Lewis and Taufic, and by Swan and his co-workers.

Dr. Delp: Dr. Skelton will give the pathologist's findings.

Pathology Report

Dr. Floyd R. Skelton, Instructor in Pathology: The role of the pathologist in the discussion of such a case as we have today seems rather straightforward. Consequently, the following report will be presented in three sections: First, the autopsy findings: second, a description of the embryologic development of the cardiac malformation; and third, a brief clinical-pathologic correlation.

At autopsy the body was that of a slightly undernourished but fairly well developed 7 year old boy with no evident cyanosis, but with a distinct pigeon-breast deformity. Since the gross examination of the organs showed that the significant lesions were confined essentially to the heart, this organ will be considered in some detail. A large interatrial septal defect was found measuring 6 by 4 cm. and located in inferior posterior portion of the septum, in such a manner that the attached margins of the septal leaflets of the mitral and tricuspid valves were approximated to form the base of the septal defect. The foramen ovale was present above the defect and, while anatomically open, was functionally closed. The great dilatation and hypertrophy of the wall of the right atrium was readily apparent and contrasted sharply with the small size and thinness of the wall of the left atrium. The pulmonary veins entered the left atrium in a normal fashion. As is usual in cases such as this, the left ventricle was small relative to the right. The leaflets of the mitral valve formed the base of the large interatrial septal defect, and careful examination of this valve failed to reveal significant morphologic changes. The valvular ring measured 8.2 cm. in circumference. The hypertrophy and dilatation of the right ventricle was also striking and was associated with dilatation of the pulmonary ring as evidenced by a circumference of 7.8 cm. In contrast, the circumference of the aortic valve was 5.2 cm. It is of interest that the pulmonary valve cusps measured 2 cm. in width, while the aortic valve cusps measured only 1.2 cm. The tricuspid valve was normal in appearance and measured 13 cm., in circumference. The ascending thoracic aorta was small, measuring 8.3 cm. in circumference above the pulmonary valve. This dilatation extended into the main branches so that the right main pulmonary artery measured 4.7 cm. in circumference and the left main pulmonary artery measured 2.7 cm. in circumference. The only other gross observation of interest was the evident hemosiderosis of the lungs and the manner in which the small branches of the

pulmonary arteries projected above the cut surface in the peripheral regions of the lungs.

An explanation for the projection of pulmonary artery radicles above the cut surface of the lung was readily apparent on microscopic examination. The walls of the arteries and arterioles were considerably thicker than normal, apparently as a result of medial muscular hypertrophy since the media showed the most marked thickening. This medial hypertrophy extended into even the smallest arterioles of the pulmonary vascular tree. When sections of pulmonary tissue were subjected to Gomori aldehyde-fuchsin stain which imparts to the elastic tissue a deep purple color, the internal elastic lamella in the pulmonary arteries and arterioles was observed to be thickened and reduplicated.

Sections of pulmonary tissue stained with hematoxylin and eosin disclosed alveoli containing many large pigment-laden macrophages. That this pigment was hemosiderin was indicated by its blue color in Perles' stain. The presence of these cells substantiated the gross morphologic and the clinical evidence of congestive cardiac failure. The bronchi contained amorphous material, and were lined by tall, columnar, mucus-containing cells resting on a greatly thickened basement membrane. The origin of these latter changes is somewhat obscure, but may be related to the repeated bouts of upper respiratory infection and pneumonia which this patient experienced over the few years of his life.

Of course, as a consequence of the protracted period of cardiac massage, some evidence of trauma would be expected in the heart and this was present as focal areas of hemorrhage in the epicardium and in fibrous connective tissue within the myocardium.

Anatomic Diagnosis

Primary. Congenital malformation of the heart consisting of an extensive defect of the interatrial septum.

Hypertrophy and dilatation of the right atrium and ventricle with dilatation of the pulmonary artery, advanced; weight of heart and lungs 770 Gm., normal 350 Gm. Normal mitral valve.

Medial hypertrophy of small and medium sized radicles of the pulmonary artery in both lungs.

Chronic passive congestion of the lungs, moderate.

Multiple subepicardial and myocardial hemorrhages (history of cardiac arrest and massage for two hours before death).

Focal atelectasis and hemorrhages in all lobes of both lungs.

Acute passive congestion of the liver, adrenals, and kidneys, slight.

It will be recalled that it is within the first few weeks of fetal life that the primitive two-chambered heart is transformed into a four-chambered organ. This is accomplished by the downward and forward growth of the septum primum from the roof of the single atrium toward the atrioventricular canal and the upward growth of the interventricular septum from the lower portion of the single ventricle. In the region of the atrioventricular canal, endocardial cushions develop, which normally unite with the septum primum and the interventricular septum, thus dividing the single atrium and ventricle into right and left chambers. The ostium primum, which is between the lower edge of the septum primum and the endocardial cushions, normally is obliterated when the septum primum and endocardial cushions fuse. Occasionally fusion does not occur. The resultant persistent ostium primum gives rise to some of the largest interatrial septal defects, such as that in the present case.

A persistent ostium primum has no effect on the heart during fetal development when the right atrial pressure is greater than the left, and when the flow of blood is normally from the right to the left atrium. However, following birth, the development of greater pressure in the left atrium than in the right leads to reversal of this flow so that the blood passes from the left to the right atrium. Coincident with the reversed flow of blood, there is greatly increased pressure within the chambers of the right heart and within the pulmonary system, so that hypertrophy and dilatation of both the right atrium and ventricle and enlargement of the pulmonary artery occur. If the

dilatation of this artery is sufficiently great, actual insufficiency of the pulmonary valve may ensue. In the pulmonary artery radicles within the parenchyma of the lungs, the medial hypertrophy and the thickening and reduplication of the internal elastic lamella is a reaction to this increased pressure in the pulmonary circulation. Of course, the blood passing from the left into the right atrium is oxygenated and, in consequence, the oxygen tension of the blood present within the right atrium, right ventricle, and pulmonary arteries is abnormally high. All of these consequences of the interatrial septal defect were manifest in the clinical examination of this patient.

Despite the increased flow of blood through the pulmonary circulation, and consequent increased return to the left atrium, this chamber does not hypertrophy because the blood readily passes into the right atrium through the large interatrial septal defect. It has been suggested[1] that the passage of blood from the left to the right atrium is not entirely due to the increased return of blood to the former chamber but that it is augmented by the fact that this chamber has a greater hydrostatic pressure by virtue of its anatomic location above the level of the right atrium.

The relatively small size of the left ventricle is commensurate with the decreased volume of blood which it is called upon to handle. The decreased output of the left ventricle, which eventuates in oxygen starvation of the systemic circulation, explains the usual underdevelopment of patients with this cardiac malformation. The decreased output is also reflected in a low systemic blood pressure and in a narrow pulse pressure, both of which were present in this case.

One is tempted to explain the murmurs in this case entirely on the basis of the cardiac malformations. Taussig[2] relates the systolic murmur and thrill either to the interatrial septal defect or to the eddy currents set up in the greatly dilated pulmonary arteries. The diastolic murmur in this patient may well have been the result of dilatation and insufficiency of the pulmonary ring, although little evidence of valvular insufficiency was visible on gross morphologic examination.

The accentuated second pulmonic sound can be explained on the basis of increased pressure within the pulmonary circulation.

No morphologic findings relative to the period of hypothermia were found, not a surprising circumstance.

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ABSTRACTS

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Abstracters

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BACTERIAL ENDOCARDITIS

Meerseman, F., Tyberbhein, J. and Lavenne, F.: Intra-auricular Communication with Mitral Endocarditis and Coronary Embolism. Acta. cardiol. **9:** 514 (Fasc. 5), (Nov.), 1954.

A case is described of a 31 year-old woman who, 5 weeks after a normal delivery, developed fever, heart failure and severe chest pain. The electrocardiogram showed a typical pattern of anterior wall infarction. The fever subsided under penicillin treatment but the patient died suddenly 7 days after admission. Autopsy showed a mitral valvulitis with vegetations characteristic of subacute bacterial endocarditis. In addition there was a large atrial septal defect so that the condition may be considered to represent Lutembacher's syndrome. The cause of death was an embolus lodged in a branch of the left coronary artery which had led to infarction of the anterior wall.

PICK

CONGENITAL ANOMALIES

DiGuglielmo, L. and Guttadauro, M.: Unusual Coronary Branch in a Case of Coarctation. Acta radiol. **42:** 141 (Aug.), 1954.

In the course of angiocardiography in a 30 year-old male with aortic coarctation an anomalous artery branch was noted to originate from the left coronary artery, and run upwards alongside the pulmonary artery. The authors presumed that this might participate as a collateral vessel to the descending aorta but were unable to definitely identify it as such.

SCHWEDEL

Wallace, H. M., Lending, M. and Rich, H.: Congenital Heart Disease in a Medical Rehabilitation Program. J. Pediat. **45:** 273 (Sept.), 1954.

Statistics are presented on the children with congenital cardiac disease, cared for under first two years of the New York City Health Department for medical rehabilitation. The group included 129 children cared for in nine separate participating hospitals. Diagnostic studies revealed slightly more than half to be operable and these children were offered surgery. Of the 66 children operated upon, 23 per cent were cured, 48 per cent improved and 17 per cent died. A discussion of ways to improve the program is presented.

HARVEY

Fowler, N. O.: Some Variations in the Clinical Picture of Congenital Defect of the Interventricular Septum. Am. J. Med. **17:** 322 (Sept.), 1954.

The clinical findings and cardiac catheterization established the diagnosis of ventricular septal defect as an isolated lesion in seven patients. In an eighth patient the clinical findings suggested ventricular septal defect but cardiac catheterization disclosed tetralogy of Fallot. In the seven instances of isolated ventricular septal defect the following clinical picture occurred:

1. A systolic murmur of maximal intensity in the second, third, or fourth intercostal spaces adjacent to the sternum was heard. In five patients a systolic thrill was felt. In three a short apical murmur or gallop was heard.

2. The pulmonic second sound varied from diminution to accentuation with splitting.

3. The pulmonary vascular markings varied from normal to accentuation with intrinsic pulsation. The cardiac x-ray silhouette was normal in two patients, showed right ventricular hypertrophy in two patients, and showed combined hypertrophy of both ventricles in three patients. The electrocardiogram was normal in three patients and showed incomplete right bundle branch block in four patients.

Cyanosis and clubbing were absent in all patients. All save one had a normal arterial saturation.

HARRIS

CONGESTIVE HEART FAILURE

Burch, G. E. and Ray, C. T.: Mechanism of the Hepatojugular Reflux Test in Congestive Heart Failure. Am. Heart J. **48:** 373 (Sept.), 1954.

Certain theoretic concepts are presented for the elevation in systemic venous pressure produced by manual pressure over the hepatic region in subjects with chronic congestive heart failure. The authors postulate that in congestive heart failure there is a generalized increase in venous tone causing venous hypertension, with the normal regulating mechanisms for venous pressure sluggish or altered in such a way that the system cannot adjust to changes in volume generally or locally while maintaining a constant venous tone. When pressure is applied externally over a large area of the venous system, as the hepatic and splanchnic areas, and blood tends to be displaced, the other segments do not distend readily but rather tend to squeeze more tightly upon the blood within, causing a further rise in venous pressure. Experiments on subjects with chronic congestive heart failure seemed to support the existence of a generalized increase in venous one in congestive failure.

MAXWELL

CORONARY ARTERY DISEASE

Sigler, L. H.: Suggestive Manifestations of Acute Coronary Occlusion or Insufficiency. Arch. Int. Med. **94:** 341 (Sept.), 1954.

A study of the early subjective manifestations of acute coronary occlusion and of coronary insufficiency was made in 1200 cases. Nine hundred seventy-four of these ran a subsequent course of myocardial infarction, and 226, of myocardial ischemia or ischemic necrosis. There was a great variation of complaints in different cases. The commonest complaint was the characteristic constricting pain, which occurred in the majority of cases. In 4.4 per cent there was no pain in any form; in 8.3 per cent the pain was felt in other areas than in the anterior chest region, and in 2.9 per cent the pain was very mild and insignificant, making a total of 15.6 per cent cases in which pain was of no help in the diagnosis. In many others the pain was not of the characteristic constricting type and was not of definite help in the differential diagnosis.

Besides pain, 62.9 per cent of patients complained of sweating; 18.2 per cent of weakness, and 7.2 per cent of other constitutional disturbances, as chills, heat sensation, flushing, and shivering. One or more cerebral symptoms, such as dizziness, light-headedness, restlessness, apprehension, faintness, syncope, and occasionally local tonoclonic movements, occurred in 21.6 per cent. Gastrointestinal symptoms, such as nausea, vomiting, gaseous eructation, "heartburn," "indigestion," and, rarely, salivation or dryness of the mouth occurred in 15.8 per cent. Respiratory symptoms, such as dyspnea, choking, difficulty in catching breath, cough, and occasionally dryness in the throat, occurred in 11.3 per cent. Complaints referable to the heart, other than pain, such as palpitation, "pounding," or "thumping," occurred in 2.4 per cent.

Early subjective manifestations of coronary insufficiency are about the same as those of coronary occlusion, except that pain in insufficiency is on the average milder and more intermittent. It is also somewhat more frequent in the retrosternal region, and its radiation to the epigastrium is less frequent. Weakness and cerebral and gastrointestinal disturbances are less frequent.

BERNSTEIN

Feldthusen, U. and Lassen, N. A.: Serum Iron after Coronary Occlusion and Traumatic Injuries. Acta med. scandinav. **150:** 53–62 (Nov. 9), 1954.

The serum iron was found to be low in all of 8 cases of acute coronary occlusion occurring concomitantly with the usual manifestations of the acute phase of the disease. Four of the patients died; the serum iron returned to normal as clinical improvement occurred in the four patients who survived. The serum iron was also studied in 10 patients who had suffered trauma. Acute hypoferremia was observed in 6 cases who had evidence of a general reaction as indicated by a feeling of discomfort, pain, pyrexia and eosinopenia. The hypoferriaemia appeared within 12 hours of the onset of the acute disorder and was found to be similar to that which has been observed after major operations, in acute and chronic infections, in terminal neoplastic disease and in a variety of other conditions. The low serum iron is felt to be a part of the general reaction of the organism to stressful stimuli.

ROSENBAUM

Bakst, A. A., Costas-Durieux, J., Goldberg, H. and Bailey, C. P.: The Physiologic Explanation of the Changes in the Coronary Circulation Precipitated by Aortic-Coronary Sinus Anastomosis. J. Clin. Invest. **33:** 1329 (Oct.), 1954.

Nonspecific cardiac procedures did not alter the quantity or character of blood flowing in retrograde fashion from the coronary artery of the normal dog.

When the coronary sinus was "arterialized" by an aorticocoronary sinus, there was a reversal of blood flow through the capillary bed and extraction of oxygen by the myocardium.

WAIFE

ELECTROCARDIOGRAPHY

Hoffman, Brian F. and Suckling, E. E.: Effect of Heart Rate on Cardiac Membrane Potentials and the Unipolar Electrogram. Am. J. Physiol. **179:** 123 (Oct.), 1954.

Papillary muscles were employed to study simul-

taneous membrane action potentials and unipolar electrograms. With this preparation it was demonstrated that timing, polarity and the magnitude of the T deflection of the electrogram depend directly on the time course of repolarization of the muscle membrane. Heart rate and duration of electric activity of the ventricle are related in a linear fashion when observed in single fibers. The authors point out that the effect of cycle length on the duration of ventricular action potentials is suggestive of an active delay of repolarization in heart muscle.

OPPENHEIMER

Little, R. C., Brody, D. A. and Tacket, H. S.: The Axostat. Am. Heart J. **48:** 721 (Nov.), 1954.

The axostat is a relatively simple instrument for rotating vector loops with respect to the "viewing" device. Axostat leads provide a number of "views" of the spatial vectorcardiogram which are not afforded by the conventional extremity leads. Using an accurately calibrated electrical model, the underlying physical principles of the axostat were tested and confirmed. The model and the tests are described. The clinical applications of the axostat described are: (1) to determine the orientation of mean spatial vectors without the necessity of measuring the areas under electrocardiographic waves and complexes; (2) to demonstrate the exceptional sensitivity with which transition-point electrocardiograms record changes due to essentially rotatory influences; and (3) to explore in various pathologic conditions of "unchartered" areas in the Burger triangle.

RINZLER

Brody, D. A.: The Meaning of Lead Vectors and the Burger Triangle. Am. Heart J. **48:** 730 (Nov.), 1954.

A closed geometric configuration, known as the Burger triangle, may be formed from the vectors of the conventional Einthoven leads. A method is presented for transforming the Burger triangle into a triangular coordinate system which obeys the Einthoven law. In general, the Burger triangle is not equilateral. A similar coordinate system may be developed for the unipolar extremity leads. The two systems may be combined into a single hexaxial reference system which obeys all the algebraic laws of the extremity leads. A scalene (nonequilateral) triangle, which represents the quantitative relationships between the electromotive forces of the heart and the extremity leads of the electrocardiogram with reasonable accuracy, may eventually supplant the equilateral triangle as a frame of reference. The concept of the lead vector introduces the powerful method of vector mathematics into certain types of electrocardiographic calculations.

RINZLER

Mangold, F. and Borter, W.: Observations on a Negative T in Lead V2. Cardiologia **25:** 107 (Fasc. 2/3), (Aug.–Sept.), 1954.

Among a total number of 5,368 electrocardiograms, 55 obtained in persons over 30 years were found, in which a T inversion in lead V_2 represented the only abnormality. Forty-eight of these were female and 7 male. These cases were submitted to further study. Conclusions drawn from this analysis were as follows.

An isolated T inversion in V_2, when found in an adult male should be always considered an indication for a thorough cardiovascular examination. A clinical abnormality is more likely in the older patients and in those with deeper inversion of T. In women, on the other hand, this finding has no significance. In two thirds of the female material having a T inversion in V_2, no abnormalities were detected on clinical examination.

PICK

Ferrero, C. and Doret, J. P.: Hemodynamic Interpretation of the U wave of the Electrocardiogram. Cardiologia **25:** 112 (Fasc. 2/3), (Aug.–Sept.), 1954.

The concept has been advanced that the U wave of the normal and abnormal electrocardiogram is related to hemodynamic factors, in particular to the early diastolic filling period of the ventricles. In order to test the validity of this concept electrocardiograms were compared before and during a Valsalva maneuver, and before and after commissurotomy in cases with mitral stenosis. Both procedures are bound to alter the amount of blood entering the ventricles early in diastole; a Valsalva test will diminish, whereas opening of the mitral ostium will increase ventricular inflow.

In 25 of 26 Valsalva tests studied in this respect, the U wave flattened out at the height of the experiment. On the other hand, in 28 out of 34 cases, in which commissurotomy was considered by the surgeon to have been accomplished to a sufficient extent, a U wave appeared in the postoperative electrocardiogram. Thus this study provides strong support to the view that the electric phenomenon of the U wave bears a close relationship to hemodynamic conditions of the ventricles.

PICK

Bordi, S.: Nomenclature and Morphology of the Electrocardiogram, A Critical Review with a Recommendation. Acta med. Scandinav. **150:** 3–23 (Supplement 295), (Aug.), 1954.

The author indicates that Einthoven's early terminology was selected on the basis of morphology and configuration rather than causation. It is his belief that the early principles of Einthoven did not guide the selection of the terms Ta and RS-T. These are said not to be single letters, to name the part of the electrocardiogram indirectly by way of a conclusion rather than directly, to fail to signify a distinct morphological character and to fail to play a part in an algebraic series such as is represented by P, Q, R, S and T. The deflections designated P, Q,

R, S and T are said to be complete ECG waves, whereas those referred to generally as Ta and RS-T are incomplete waves. The author writes extensively concerning the objections to the terms Ta and RS-T and considers these symbols inappropriate, ambiguous and misleading and he recommends that their use be discontinued. It is suggested that the Greek letter Φ (Phi) be used to replace Ta and the Greek letter Θ (Theta) be used to replace the symbol S-T segment.

ROSENBAUM

Tannenbaum, O., Vesell, H. and Schack, J. A.: The Spatial Vectorballistocardiogram. Am. Heart J. **48:** 562 (Oct.), 1954.

By means of a direct-body pickup utilizing a coil and magnet, the headward-footward, lateral, and anteroposterior movements of the body were simultaneously recorded with Lead 1 of the electrocardiogram on a four-channel direct-writing oscillograph. The vectorballistocardiogram was successively recorded in the frontal, sagittal, and horizontal planes of the body by means of a cathode ray oscilloscope. The spatial vectors corresponding to the H, I, and J waves of the ballistocardiogram were found to be related to the anatomic position of the heart; on the other hand, there was no correlation of the K and L vectors with cardiac position. The possible significance of vectorballistocardiography in relation to the usual method of longitudinal scalar recording of the ballistocardiogram was discussed.

RINZLER

Edeiken, J.: Elevation of the RS-T Segment, Apparent or Real, in the Right Precordial Leads as a Probable Normal Variant. Am. Heart J. **48:** 331 (Sept.), 1954.

Ten examples of apparent high elevation of the RS-T segment in the right precordial leads, without other evidences of heart disease, were presented. The presence of this pattern initially suggested injury to the myocardium, but this opinion was considered untenable because (1) in all cases on reexamination, the RS-T segment persisted longer than usual in cases with proved acute injury of the heart. In four cases the pattern persisted longer than 5 years. (2) No evidence was found to indicate a previous myocardial infarction and subsequent ventricular aneurysm, pericarditis, and endocrine or metabolic disorder. (3) Eight of the patients had no symptoms in any way suggestive of cardiac disease; two had symptoms somewhat suggestive of angina pectoris, but subsequent examinations disclosed other bases for their symptoms and no supporting evidence of heart disease. No physiological explanation for the phenomenon was offered. It was felt that this pattern could be considered as a possible normal variant if careful study, including unchanging serial electrocardiograms, reveals no corroborative evidence of heart disease.

MAXWELL

Klakeg, Clayton H., Berry, Anna M. and Burchell, Howard B.: Duration of QT Interval at Slow Ventricular Rates. Am. J. Physiol. **179:** 159 (Oct.), 1954.

When the rate is below 50 per minute the Q-T interval is inversely related to frequency although there is a marked scatter. The correlation is better for patients under 50 years without obvious heart disease than in the age group above this. Mean Q-T indices were rather similar whether hearts were normal or not. The same was true of Q-T ranges. Q-T indices were over 0.42 in 10 per cent of cases. Incomplete block with varying A-V conduction was observed to have a slightly longer Q-T interval after a long cycle as compared to the one following a short cycle. It was emphasized that during a bradycardia other factors beside rate are important in determining the Q-T interval. Q-T interval and duration of mechanical systole are not always the same.

OPPENHEIMER

Kalliomäki, L.: Some Clinical Observations on Patients with Electrocardiographic Signs of Left Ventricular Hypertrophy. Acta med. scandinav. **150:** 223–226 (Fasc.), (Aug.), 1954.

The author collected a series of 100 patients on the basis of consecutive electrocardiograms which demonstrated the signs of left ventricular hypertrophy according to the criteria of Sokolow and Lyon. These patients were compared with a control series of 100 patients of similar age grouping whose electrocardiograms failed to show such evidence. In the study group 71 patients had hypertension, eight patients had aortic valvular disease and 12 had heart failure due to myocardial fibrosis. In 13 cases of the study group there was no definite or satisfactory explanation for the electrocardiographic evidence of left ventricular hypertrophy although the blood pressure levels were borderline in several of them. In the control group, 28 patients had hypertension. The body weight of the patients in the two groups was essentially the same. Roentgenographic studies of the heart were normal in 49 cases of the study series and in 91 patients of the control series.

ROSENBAUM

Rakita, L., Borduas, J. L., Rothman, S. and Prinzmetal, M.: Studies on the Mechanism of Ventricular Activity. XII. Early Changes in the RS-T Segment and QRS Complex Following Acute Coronary Artery Occlusion: Experimental Study and Clinical Applications. Am. Heart J. **48:** 351 (Sept.), 1954.

Epicardial, intramural and cavity leads showed S-T segment elevation in ischemic regions, beginning within 30 to 60 seconds after ligation of a major coronary artery and reaching a maximum amplitude in 5 to 7 minutes. The amplitude of the simultaneously recorded tracings diminished from epicardium to cavity. QRS complex alterations of similar direction accompanied the S-T segment deviation.

Injuries produced by coronary artery ligation appeared to be broader intramurally than at the epicardium. S-T segment depression occurred over the injured area when the heart was exposed for several hours and over the normal myocardium opposite to the injured region.

MAXWELL

Mitchell, J. H. and Shapiro, A. P.: The Relationship of Adrenalin and T-Wave Changes in the Anxiety State. Am. Heart J. **48:** 323 (Sept.), 1954.

The mechanism of T-wave inversion in an emotionally unstable patient without demonstrable heart disease was studied by means of continuous electrocardiographic tracings. Electrocardiographic changes consisting of S-T segment depression and T-wave inversion occurred during a variety of psychic stimuli and anxiety-producing situations, venipuncture, and immediately following the injection of very small doses of Adrenalin (0.025 cc. of 1:10,000 solution) into a constant infusion without the patient's knowledge. The same abnormalities followed the injection of Adrenalin while the patient was breathing 100 per cent oxygen and after the administration of nitroglycerine. None of the same procedures produced significant electrocardiographic changes in 2 normal subjects or in a patient with an intermittent arrhythmia.

It was felt that in certain individuals the myocardium is particularly sensitive to the effect of Adrenalin and these effects can be evoked by anxiety-producing stimuli. The mechanism by which Adrenalin produces these changes is probably not related to blood flow through the coronary arteries but seems more likely due to a direct effect of Adrenalin on the myocardium.

MAXWELL

ENDOCRINE EFFECTS ON CIRCULATION

Steinitz, K.: The Clinic Value of Radioactive Iodine Tests for the Assessment of Thyroid Function, Acta med. scandinav. **149:** 187–200 (July 8), 1954.

The author studied nearly 200 cases by means of (a) urinary excretion of radioiodine in three separate periods, (b) the 48 hour/2 hour ratio of plasma I^{131} (Blondel index), and (c) the protein-bound I^{131} of the plasma 48 hours after ingestion of the tracer material. A low urinary excretion was a constant finding in hyperfunction of the thyroid gland. However, low excretion may be only an expression of avidity of a goitre for iodine and is not always clearly related to hyperactivity. The urinary excretion values showed considerable overlapping in the euthyroid and hypothyroid cases. The 48 hour/2 hour ratio of radioiodine in the plasma and the protein-bound I^{131} at 48 hours showed quite sharp divisions in values between normal and thyrotoxic subjects. The former cannot be used in the diagnosis of hypofunction of the thyroid gland. It is recommended that surgical therapy of toxic goitre without previous examination with I^{131} tests be reserved only for fully developed classical cases. It is suggested that at least one iodine fixation test and one hormone secretion test be done simultaneously in all other cases to avoid operation in cases of extrathyroid hypermetabolism and to evaluate the diagnostic possibilities more carefully.

ROSENBAUM

HYPERTENSION

Storstein, O. and Tveten, H.: The Effect of Hexamethonium Bromide on the Pulmonary Circulation. Scandinav. J. Clin. & Lab. Invest. **6:** 169–177 (No. 3), (July 15), 1954.

Fourteen patients with various types of heart disease were given hypotensive doses of hexamethonium bromide during cardiac catheterization. Distinct decreases in the blood pressure were recorded in the systemic arteries, the pulmonary artery and the pulmonary capillaries and there was an associated reduction in the cardiac output. The heart rate and systemic and pulmonic resistance were unaffected. The drop in cardiac output was attributed to either dilatation of the peripheral blood vessels with pooling of blood in the systemic veins and capillaries and a reduction in venous return or reduced sympathetic tone of the heart muscle with decreased contractility. It was reasoned that if the effect of hexamethonium bromide was on the tone of the pulmonary arterioles, the fall in the pulmonary artery pressure should exceed that in the pulmonary capillary venous pressure. Since the fall was the same, it is concluded that the effect of hexamethonium bromide is an expression of reduction of the pressure in the left atrium and left ventricle rather that any active dilatation of the pulmonary arterioles.

ROSENBAUM

Stroia, L. N., Bohr, David F. and Vocke, L.: Experimental Hypertension in the Hamster. Am. J. Physiol. **179:** 154 (Oct.), 1954.

Systolic blood pressure at the ankle in the hamster averaged 108 mm Hg. This compared well with average carotid pressure which was 111 mm Hg. Hypertension was easily produced by a constricting figure-of-eight around the kidney or by desoxycorticosterone acetate and one per cent salt solution. This latter solution produced a pronounced water turnover.

OPPENHEIMER

Kleh, J., and Fazekas, J. F.: The Use of Reserpine in the Hypertensive Arteriosclerotic Syndrome. Am. J. M. Sc. **228:** 560 (Nov.), 1954.

A series of 8 patients with diastolic hypertension and evidence of arteriosclerotic cerebral vascular disease was studied by means of the usual clinical indices and the nitrous oxide method for cerebral blood flow. The data were obtained before and after the administration of Serpasil therapy to maximum

blood pressure depression dosage. The peak dose employed was 4.0 mg. In all cases there was a significant depression of the effective blood pressure in all subjects. There was no improvement in any of the signs and symptoms attributed to vascular insufficiency in any of the patients at the dosage levels studied. Despite the blood pressure effects observed, there was no significant change in cerebral blood flow, cerebral metabolic rate or vascular resistance. It would seem that Serpasil alone is of little value in the treatment of hypertensive arteriosclerotic patients.

SHUMAN

Wilkins, R. W.: Rauwolfia in the Treatment of Essential Hypertension. Am. J. Med. **17:** 703 (Nov.), 1954.

Rauwolfia constitutes a distinct addition to the drug therapy of hypertension. Its definite relaxing, calming or tranquilizing action is most gratifying to hypertensive patients who typically are troubled by anxiety, irritability, aggressiveness and compulsiveness. A sense of relaxed well being, improvement in personality, and relief of the ordinary symptoms of headache, palpitation, fatigue and anxiety can be expected to occur in almost every patient. The hypotensive action of rauwolfia, although slow and moderate, is real. The bradycardia is also definite and is helpful in counteracting the tachycardia produced by hydralazine.

Perhaps the greatest usefulness of rauwolfia is in combination with the more powerful hypotensive agents with which it serves as an adjunct or background agent. Because of this additive or snyergistic effect it is possible not only to use lesser doses of the powerful agents effectively but also to make their actions more acceptable to the patient. Without Rauwolfia, hydralazine and hexamethonium are very difficult to use.

Rauwolfia is useful in maintaining a normal or almost normal blood pressure in patients in whom this result has already been achieved but only by a combination of rauwolfia with other drugs. It will maintain a blood pressure at a lower level in many patients in whom it is ineffective alone in achieving that level. Likewise, rauwolfia will maintain normotension in many "prehypertensive" members of known hypertensive families, who have the typical labile neurogenic vasomotor responses characteristic of this group. Whether or not this "preventive" use of the drug is really worthwhile will be shown only by long-term studies.

HARRIS

Finnerty, F. A.: The Value of Rauwolfia Serpentina in the Hypertensive Patient. Am. J. Med. **17:** 629 (Nov.), 1954.

After treating 89 hypertensive patients with rauwolfia alone and in combination with other potent hypotensive agents, the author concludes that Rauwiloid is definitely superior to mild barbiturate sedation for the reduction of blood pressure and for the relief of anxiety in patients with normal eyegrounds or with grade 1 hypertensive retinopathy. When added to Veriloid, Rauwiloid frequently made possible a reduction in the dose of Veriloid by one-third or more, thus reducing significantly the incidence of nausea and vomiting, and also enhancing the hypotensive effect. When added to hexamethonium and Apresoline in severe hypertension, Rauwiloid made possible a reduction in the hexamethonium dosage by one-third or more in all but five cases, and eliminated the need for Apresoline entirely in all but four cases. The blood pressure remained the same or improved. The hexamethonium- and Apresoline-induced side effects were either greatly reduced or eliminated altogether.

In addition to its hypotensive effects, Rauwiloid also produced bradycardia, true weight gain, general feeling of well-being, and relief of headache and anxiety.

HARRIS

Perry, M. H. Jr. and Schroeder, H. A.: Studies on The Control of Hypertension by Hyphex III. Pharmacological and Chemical Observations on 1-Hydrazinophthalazine. Am. J. M. Sc. **228:** 396 (Oct.), 1954.

It has been shown that the combination of hexamethonium and hydrazinophthalazine lowers the blood pressure of hypertensive patients. Because the latter compound can cause collagen diseases, the clinical and pharmacological reactions which might occur with it in the body have been studied. The actual combination of Apresoline with mercaptans in body fluids has been described. *In vitro* studies revealed no reaction between the drug and several steroid substances. However, the clinical use of Apresoline resulted in a decrease in serum cholesterol after the inception of therapy; this effect was partially dissipated after a period of 6 months. The hydrazine compounds reacted with certain trace metals including iron and copper. This is of interest in view of the tendency for a moderate anemia to develop during the course of therapy with Apresoline. Anemia was not observed in patients taking hexamethonium alone. Pherentasin obtained from extracts of hypertensive blood was shown to be completely inert in the presence of therapeutic concentrations of Apresoline. Pherentasin is believed to contain a carbonyl group which may represent the site of its inactivation by the drug since Apresoline was shown to have an affinity for certain carbonyl compounds in the present study.

SHUMAN

Dahl, L. K., Stall, B. G. III and Cotzias, G. C.: Metabolic Effects of Marked Sodium Restriction in Hypertensive Patients. Changes in Total Ex-

changeable Sodium and Potassium. J. Clin. Invest. **33:** 1397 (Oct.), 1954.

Eleven patients with essential hypertension were given a low sodium diet supplemented during control observations with 10 Gm. of enteric coated sodium chloride daily. This supplement was removed during the experimental period and certain physiological studies were performed.

No correlation was found between changes in blood pressure and sodium or potassium restriction. These studies confirm others which show that sodium restriction does not act by simply salting out.

Furthermore, some of the variations occurring in total exchangeable sodium or potassium were probably due to fluctuations in the amount of these electrolytes available for exchange with the isotopes Na^{24} and K^{42}, presumably due to the reservoir in bone.

WAIFE

Tobian, L. Jr. and Binion, J.: Artery Wall Electrolytes in Renal and DCA Hypertension. J. Clin. Invest. **33:** 1407 (Oct.), 1954.

These authors had previously demonstrated an abnormally large amount of sodium and water in the renal artery of hypertensive subjects at post mortem. In this study the sodium content of the aorta of rats with surgical renal hypertension was significantly increased above normal. The sodium changes cannot be accounted for merely as an increase in extracellular fluid. The chloride content was unchanged. Aortas from hypertensive rats also had more potassium and less magnesium than normal.

Similar findings were noted in rats made hypertensive by administration of desoxycorticosterone acetate (DCA). Thus the aortas show the same chemical alterations in both renal and DCA hypertension.

No uniform response to DCA administration was found in all tissues. The skeletal muscle potassium decreased, but increased in the aorta and increased considerably in the brain.

WAIFE

Corcoran, A. C., Dustan, H. P., Taylor, R. D. and Page, I. H.: Management of Hypertensive Disease. Am. J. Med. **17:** 383 (Sept.), 1954.

Reviewing the pharmacotherapy and management of severe hypertensive disease, the authors report that Hydralazine gave sustained relief and decreased mortality in about half of their patients treated with this drug. Its use was complicated by common, usually transitory side-effects and, in some patients, by a delayed toxic response characterized as a rheumatic and febrile response. Experience with hexamethonium indicated temporary relief in 16 of 17 patients with malignant hypertension; the duration of relief was limited by tolerance to its depressor effect on supine diastolic pressure. Benefit was not determined by persistence of orthostatic hypotension. Some additive effects of combined hexamethonium-hydralazine therapy were defined in 7 of 14 patients tested with these drugs separately and in combination. Only two gained more than 10 mm Hg decrease in average supine diastolic pressure from the combination. Side-effects of Hydralazine were not mitigated by effective doses of hexamethonium. Preliminary observations indicate that reserpine (Serpasil) is a potent antipressor in some patients when used alone or in association with other drugs.

The considerable efficacy of specific agents and procedures in some patients, but not in others, suggests that hypertension in these is sustained by different, definable mechanisms. Insight into these should diminish the large measure of poorly rationalized empiricism which presently clouds the treatment of hypertensive disease. Treatment should do no harm and should be applied early enough in the course of the disease since to delay too long may be to treat too late.

HARRIS

Schissel, D. J. and Larson, E.: Inquiry Into Role of Antihypertensive Drugs. Arch. Int. Med. **94:** 438 (Sept.), 1954.

The majority of hypertensive patients do not need treatment with "antihypertensive" agents. Many will respond satisfactorily to symptomatic therapy. Others, with mild hypertension, need no treatment at all. Treatment with the antihypertensive agents should be reserved for those patients whose response to symptomatic treatment is inadequate and in whom the hypertension is progressive and is producing organic changes. Hydralazine and hexamethonium chloride, alone or in combination, are drugs that will lower blood pressure to normal levels with relief of symptoms in most patients who fail to respond to symptomatic therapy. Patients vary in their response to each of these agents, and there is no way to predict which drug will be more efficacious in the individual patient. Many patients respond equally well to either Hydralazine or hexamethonium chloride. Hexamethonium chloride, because of its ease of administration, is preferred to the parenteral preparation and in most patients gives as good a response.

BERNSTEIN

Harris, R. and Phelan, J. J.: Treatment of Elderly Hypertensive Patients with Hydralazine (Apresoline) Hydrochloride. Geriatrics **9:** 431 (Sept.), 1954.

Prolonged administration of Hydralazine to 26 elderly hypertensive patients, with an average age of 67.3 produced a significant arterial blood pressure drop of 20 mm. of mercury or greater in 18 subjects (69.2 per cent).

The clinical condition of 9 patients under 71 improved as their blood pressures became more normal.

Electrocardiographic improvement followed in 6 of these 9. Eleven showed definite cardiac, cerebral, or renal deterioration. Tachycardia and congestive heart failure were attributed to the use of Hydralazine rather than to the lowered blood pressures. The clinical condition of 6 patients remained unchanged during therapy.

The chief indication for treatment of hypertension in elderly patients is an elevated diastolic blood pressure with disabling symptoms which constitutes a threat to the patient's health. Since best results and fewest complications occurred in patients below 71, treatment of elderly hypertensive people above this age does not appear advisable. It is recommended that reserpine (Serpasil) be used to initiate therapy, and if necessary, Hydralazine may then be added cautiously. Contraindications to the use of Hydralazine include congestive heart failure, severe coronary artery disease, significant cerebral disease, or advanced renal insufficiency.

RINZLER

Tuchman, H., Sletten, I. W. and Crumpton, C. W.: A Clinical Study of the Effects of Intravenous Reserpine (Serpasil) in Hypertensive Patients. Am. Heart J. **48:** 449 (Sept.), 1954.

The effect of a single intravenous injection of Reserpine was studied in 23 hospital patients with moderate to severe hypertension. In 13 of these patients there was a fall in blood pressure to normotensive levels and/or a reduction in calculated mean arterial blood pressure of 20 mm. Hg or more. Nineteen of the 23 patients experienced mild side effects characterized by nasal stuffiness, facial flush, and lethargy. A Sodium Amytal test was performed in 15 of the 23 patients and the blood pressure response was compared with the effect of intravenous reserpine. Generally, patients in whom the mean arterial blood pressure fell 20 mm. Hg or more with sodium Amytal showed a comparable blood pressure reduction following intravenous reserpine.

MAXWELL

Rosenfeld, S., Thomas, H. V. and Drury, D. R.: Effects of Renal Denervation on Cerebral Hypertension in the Rabbit. Am. J. Physiol. **178:** 392 (Sept.), 1954.

Hypertension was produced in the rabbit by restricting blood flow to the head without involving the carotid sinuses. Renal denervation lowers the elevated blood pressure. It is pointed out that the effectiveness of splanchnic section and of sympathectomy may depend on the degree of renal denervation.

OPPENHEIMER

Perry, H. M. Jr., Schroeder, H. R. and Morrow, J. D.: Studies on the Control of Hypertension by Hyphex. IV. Levels of the Agents in Urine and Blood. Am. J. M. Sc. **228:** 405 (Oct.), 1954.

Measurement of the urinary and blood levels of hexamethonium administered orally and parenterally to hypertensive subjects revealed that about 6 per cent of a single oral dose is excreted in the urine, half within 6 hours. The excretion on continuous parenteral dosage is about 10 times that obtained on oral administration. Therapeutic concentrations in plasma averaged 0.37 mg. per 100 cc. with levels as high as 16 mg. found in an azotemic patient. Acute toxic symptoms of the drug were autonomic paralysis and hypotension while chronic toxicity produced tachypnea due to chronic pulmonary fibrosis.

The excretion level of the hydrazine compound was 1.1 per cent of the free drug on continuous oral therapy. However, an additional portion was excreted in bound form presumably associated with mercaptan. This latter fraction decreased as therapy progressed as though the body stores of sulfhydryl were being depleted. The dihydrazine derivative was not recovered in the urine as such. Therapeutic plasma levels of Apresoline averaged 0.023 mg. per 100 cc. Acute toxic manifestations included asthenia, nausea and vertigo. In two years, no instance of tolerance to the hypotensive action of Hyphex has been observed.

SHUMAN

Friedman, S. M., Nakashima, M. and Friedman, C. L.: Further Evidence for Depressor Effect of Pitressin Hormonal Hypertension. Am. J. Physiol. **179:** 165 (Oct.), 1954.

Rats were made hypertensive with desoxycorticosterone acetate. These animals then received daily subcutaneous injections of Pitressin. A transient rise in blood pressure at one-half hour was followed by a return to control values at three hours. This effect is present even though the injections were continued for eight days. After the third hour a depressor effect was observed with its maximum at five to seven hours. This action became more pronounced as the number of injections increased.

OPPENHEIMER

PATHOLOGIC PHYSIOLOGY

Ask-Upmark, E.: On the "Pulseless Disease" outside of Japan. Acta med. scandinav. **149:** 161–178 (July 8), 1954.

The author reviews the Takayashu syndrome or pulseless disease which was believed, at first, to occur only in Japan, and reports that he has assembled 30 cases observed outside of Japan, four of them studied by himself. The disorder is a chronic, progressive, obliterative brachiocephalic arteritis which deprives the upper half of the body of its blood supply. Secondarily, there develops a collateral arterial blood supply in the upper half of the body. The involvement of the arteries is a panarteritis, involving all layers of the arterial wall and ultimately producing obliteration. The ischemia of the upper half of the body results in weakness and pains in the arms, especially after their use, absent pulses and blood

pressure, neurological changes such as hemiplegias, aphasia and mental impairment and disturbances in the eyes. The development of collateral circulation results in palpable superficial arteries, vascular murmurs and crenations of the ribs. Increased sensitivity of the carotid sinus is a common feature of the cases. In a number of the recorded cases there has been arterial hypertension in the lower extremities, although the mechanism of this change is not clear. Tachycardia, fever and an increased erythrocyte sedimentation rate are other abnormal signs commonly observed in these patients. There is a marked predilection for females. The course of the disease is usually chronic but the prognosis is poor. Death results from cerebral or renal disease or complicating disorders.

ROSENBAUM

Stroud, Robert C. and Conn, Hadley L., Jr.: Pulmonary Vascular Effects of Moderate and Severe Hypoxia in the Dog. Am. J. Physiol. **179:** 119, (Oct.), 1954.

Cardiac output was determined by a radioisotope dilution technique. Anoxia was produced by allowing dogs to breathe mixtures of five and ten per cent oxygen in nitrogen. The former mixture represented 46 per cent saturation and the latter 79 per cent. Both increased resistance to blood flow through the lungs. This was considered to represent vasoconstriction. Isotope dilution curves furnished no support for the presence of pulmonary arterio-venous shunts during anoxia. A small increase in pulmonary blood volume was observed during anoxia.

OPPENHEIMER

Still, J. W. and Whitcomb, E. R.: An Investigation of Renal Shunts in Rats. Am. J. Physiol. **178:** 399 (Sept.), 1954.

These anatomical studies demonstrate the possibility of intermittent flow in rat kidneys. Evidence for glomerular intermittence and juxtamedullary and other shunts is presented. Caution is urged in the physiological interpretation of these findings. Changes in flow patterns are demonstrated. It is possible that renal function may be adjusted in this manner.

OPPENHEIMER

Himbert, J., Theard, A., Gele, P. and Scebat, L.: Renal Hemodynamics in the Course of Chronic Constrictive Pericarditis. Arch. mal. coeur **47:** 733 (Sept.), 1954.

Renal function tests and calculations of renal hemodynamics in 15 cases with chronic constrictive pericarditis are reported. Nine were submitted to pericardectomy; 3 died during or immediately after the operation, while in 6 marked improvement was evidenced by the disappearance of dyspnea and edema, marked increase in diuresis, reduction of venous, right auricular and pulmonary wedge pressures and augmentation of cardiac output. While surgery is followed by marked improvement of the reduced renal blood flow, this is not always true, as far as the pre-operative impairment of glomerulus filtration is concerned.

The disturbance of renal circulation in the course of constrictive pericarditis seems to be largely due to the impairment of cardiac output. The role of elevation of venous pressure in the kidneys is not entirely clear but it may be responsible for associated disorders of kidney function, viz., water and sodium excretion. The latter cannot be ascribed merely to the depression of glomerulus filtration because its reduction does not invariably cause edema formation in constricted pericarditis, and, conversely, improvement of glomerulus filtration does not necessarily accompany disappearance of edema after surgery. The conclusions are in keeping with results of another similar study in 66 cases with valvular heart disease.

PICK

Berglund, E.: Ventricular Function VI: Balance of Left and Right Ventricular Output; Relation Between Left and Right Atrial Pressures. Am. J. Physiol. **178:** 381 (Sept.), 1954.

These experiments examine the relationship between right and left atrial pressures. When the outflow resistance of one ventricle is increased its filling pressure is increased as compared to the other ventricle. Occlusion of a coronary artery elevates the filling pressure on that side. Pressures in the atria, varying according to Starling's Law, explain how the ventricular outputs are integrated with each other. Right atrial pressure is not a valid indicator of left ventricular function. Each ventricle must be studied separately.

OPPENHEIMER

Smythe, C. McC., Gilmore, J. P., Maloney, J. V., Jr. and Handford, S. W.: An Analysis of the Direct Hydraulic Effect of Intra-Arterial Transfusion. Am. J. Physiol. **178:** 412 (Sept.), 1954.

As a result of these experiments the authors conclude that the hydraulic effect of intra-arterial blood transfusion dos not explain its clinical usefulness in the treatment of shock. The pressure elevation may be predicted by the product of the infusion rate and the existing peripheral resistance.

OPPENHEIMER

Gilson, A. S. and Keyananda, P.: Retrograde Transmission Across the A-V Junction of the Turtle Heart. Am. J. Physiol. **178:** 375 (Sept.), 1954.

Normal pacemakers were destroyed in rabbit hearts to make them non-rhythmic. In these preparations a single impulse or a series of impulses will be transmitted from ventricle to atrium as well as in the usual direction.

OPPENHEIMER

Hoelscher, B.: Effect of Adrenalectomy on Cardiac Output of Parabiotic and Single Rats. Am. J. Physiol. **179:** 171 (Oct.), 1954.

When one of a pair of parabiotic rats is adrenalectomized the adrenals of the other one of the pair were observed to hypertrophy. The heart and thymus weights were different between the parabionts after one had both adrenals removed. Adrenalectomized parabionts had a greater depression in cardiac output than that seen in adrenalectomized rats. The author discusses a parabiotic concerned with transmission of adrenal steroids through the anastomosis.

OPPENHEIMER

Ravin, H. A., Denson, J. R. and Jensen, H.: Electrolyte Shifts and Electrocardiographic Changes During Tourniquet Shock in Rats. Am. J. Physiol. **178:** 419 (Sept.), 1954.

Tourniquet shock was produced in a standard manner in rats. After lethal shock and removal of the constrictions the injured muscles were observed to have a rapid accumulation of extracellular fluid and intracellular sodium. Intracellular potassium fell progressively but calcium and magnesium were not significantly changed. Heart muscle lost sodium and gained potassium although calcium, magnesium and water were unaltered. When voluntary muscle was uninjured the changes after less severe shock were similar to those stated above. When edema was forming rapidly in damaged tissues the serum sodium was briefly depressed. Potassium in serum was elevated to 160 per cent and rose to 200 to 220 per cent postmortem. Serum calcium was elevated early after the tourniquets were released but magnesium was variable. Late in shock the electrocardiogram presented changes similar to those seen with elevated potassium. Injection of potassium was poorly tolerated although the myocardium was still sensitive to this ion. The authors stress the depletion of intracellular sodium as a mechanism in the genesis of shock.

OPPENHEIMER

Schaub, F., Bühlman, A. and Kälin, R.: The "Cor Kyphoscolioticum" and its Pathogenesis. Cardiologia **25:** 146 (Fasc. 2/3), (Aug.–Sept.), 1954.

On the basis of data obtained in pulmonary function studies and by cardiac catheterization in 16 cases with kyphoscoliosis, the authors discuss the pathogenesis of the cor kyphoscolioticum. Neither clinical nor anatomical findings in this condition, whether right ventricular hypertrophy and dilatation or right heart failure, can be ascribed solely to the mechanical impedance to circulation caused by the deformity of the thorax and the associated displacement of the heart and of the big vessels. It rather appears that respiratory failure caused by the immobility of the chest, and secondary hypoventilation with hypoxia and hyperkapnea lead to pressure elevation in the pulmonary circulation and thus eventually to failure of the right heart. Prognostic and therapeutic implications based on this concept are discussed.

PICK

Johansson, L., Malmström, G. and Uggla, L. G.: Intracardiac Knotting of the Catheter in Heart Catheterization, J. Thoracic Surg. **27:** 6 (June), 1954.

Serious complications of heart catheterization appear to be rare. Previously writers have pointed out the importance of avoiding looping and kinking of the catheter in its passage through the heart. A previous case was presented in which kinking of the distal end of the catheter caused it to be arrested at the axillary level and necessitated surgical intervention for its removal.

The authors' search of the literature reveal no reports of more complicated coil or knot formation. They have therefore described three cases of intracardiac knotting of the catheter. Two of the knots formed in the same patient, before and after surgical treatment of constrictive pericarditis. In the third instance a No. 9 catheter formed a large loop in the right ventricle.

In two of the situations it was necessary to employ a general anesthetic. The authors' point out that constant effective fluoroscopy is essential for preventing intravascular knotting of the catheter. Coiling and looping must be avoided. Should a knot form, withdrawal of the catheter would appear to be facilitated by anesthetization of the patient. It is significant that in the three cases reported, this number represented 3 of 12 catheterizations performed on patients with constrictive pericarditis.

DENNISON

Brown, C. C., Fry, D. L. and Ebert, R. V.: The Mechanics of Pulmonary Ventilation in Patients with Heart Disease. Am. J. Med. **17:** 438 (Oct.), 1954.

Using intraesophageal pressure, recorded by a specially designed balloon, as an index of intrathoracic pressure, the authors studied pressure-volume relationships in the lungs of normal human subjects and patients with heart disease. A high correlation was demonstrated between the reciprocal of the vital capacity and the pressure change per 100 cc. change in lung volume both in normal subjects and patients with heart disease. Pressure-flow curves obtained from patients with heart disease when breathing air and argon-oxygen demonstrated that tissue friction was a negligible factor and that the resistance to movement of the lungs was caused by resistance to gas flow. Resistance to air flow was found to be increased in certain patients with heart failure and normal in other patients. No correlation was found between resistance to air flow and reduction of vital capacity in these patients.

Since there may be no increase of resistance to air

flow in patients with cardiac disease and exertional dyspnea, it appears that exertional dyspnea is most closely related to the reduction in vital capacity and altered elastic properties of the lung. On the other hand, it is likely that increased resistance to air flow plays an important role in the dyspnea of cardiac asthma.

Of several explanations for the alteration of the elastic forces and the diminution of vital capacity in patients with heart disease, the most likely theory, suggested by von Vasch, is that an increase in the rigidity of the lung tissues results from the increase in the pulmonary capillary pressure in the lungs of patients with heart disease. An additional factor contributing to this alteration of the elastic properties of the lung tissues is interstitial edema secondary to the increased pulmonary capillary pressure.

HARRIS

Wilson, R. H., Hoseth, W., Sadoff, C. and Dempsey, M. E.: Pathologic Physiology and Diagnostic Significance of the Pressure Pulse Tracings in the Heart in Patients with Constrictive Pericarditis and Pericardial Effusion. Am. Heart J. **48:** 671 (Nov.), 1954.

The pressure tracings obtained by right catheterization are described in 10 patients with constrictive pericarditis and three patients with acute pericardial effusion. The data so obtained were reviewed against a background of catheterization data of 453 patients with other forms of cardiac disease. The cardiac index was reduced in all patients with constrictive pericarditis. The right-ventricular diastolic-to-systolic pressure ratio was greater than 40 per cent in all patients with constrictive pericarditis. This was true in only 2.4 per cent of 453 patients with cardiac disease other than constrictive pericarditis. In the latter group only 0.7 per cent had the combination of the dip and high ratio, whereas this occurred in 92 per cent of the patients with pericardial disease. The difference between the pulmonary-arterial diastolic and right-atrial mean pressures was consistently diminished in patients with pericardial disease, but this was observed less frequently in those with other forms of cardiac disease with right-heart failure. The early rapid rise in the diastolic-filling pressure to form a plateau in the right-ventricular pressure tracing is characteristic but not specific for constrictive pericarditis.

RINZLER

Spencer, M. P.: Acute Effects of Moderate Increases in the Hematocrit on the Hemodynamics of the Normal and Denervated Kidney. Am. J. Physiol. **178:** 462 (Sept.), 1954.

Renal sympathectomy does not produce a change in total or segmental renal vascular resistance during the first 2 to 24 hours. The presence or absence of anesthesia is not a factor. When animals are made moderately polycythemic with washed red cell concentrates renal blood flow is maintained in innervated kidneys. Under the same experimental circumstances renal blood flow is decreased in the denervated kidney. When adjustments are made for viscosity changes there are indications of dilation of renal vessels in the normally innervated kidney. Increased blood pressure did not result from red cell infusion and hence can not account for a failure of blood flow to decrease when the hematocrit was increased. Glomerular filtration rate was moderately increased and the filtration fraction rose markedly in normally innervated kidneys. As a result intraglomerular pressure was increased. This indicates afferent arteriolar dilation. This is similar to what is seen in polycythemia where flow actually goes above control values. This dilator mechanism is depressed by anesthesia and the denervation in acute experiments. The author is of the opinion that no extrinsic nervous mechanism need be considered in relation to maintained renal blood flow in long sustained polycythemia. The role of changes in hematocrit in producing variations in filtration fraction is emphasized. This factor must be considered when renal clearances are studied.

OPPENHEIMER

Margolin, S., Lu, G., Yelnosky, J. and Makovsky, A.: Antiaccelerator and Antiarrhythmic Cardiac Action of Synthetic Steroid Alkamines. Science **120:** 576 (Oct. 8), 1954.

This is a brief report on the pharmacologic properties of an interesting compound; a synthetic steroid alkamine, with the chemical formula, 16-cyclohexylamino-allopregnandiol, or Sch 2684.

Auricular fibrillation induced by local application of Mecholyl plus pinching of a dog's heart was consistently arrested or prevented by this drug. This substance was apparently superior to intravenous quinidine, and ventricular tachycardia or fibrillation was not observed. The drug also antagonized auricular arrhythmias induced in dogs by intracardiac injection of aconitine, as well as ventricular tachycardia produced by ouabain or coronary ligation.

No significant electrocardiographic changes were noted after effective doses. The drug showed no anti-histamine activity or antispasmodic action on the gastro-intestinal tract. Anticholinergic action was not demonstrated and the pressor response to epinephrine was not blocked.

This substance appears to have a rather selective adrenolytic action against epinephrine in the heart. This site of this activity may be the sinus node. The cardiac antiaccelerator properties of this drug suggests its possible use in sinus tachycardia and in other states of rapid heart action.

WAIFE

Carlsten, A.: On the Vegetative Control of Auricular and Ventricular Rates and Rhythms in Total Heart Block. Acta med. scandinav. **149:** 270–186 (July 15), 1954.

In 15 cases of complete atrioventricular block the

author studied the effects of changes in posture and the influence of vegetative drugs to elucidate the supposed connection of the auricles and ventricles and to compare the auricular and ventricular responses to these variations. A distinct sinus arrhythmia was present in 11 cases and the P–P interval containing a ventricular complex was characteristically among the shortest. The sinus arrhythmia always disappeared with standing. The effect of Skopyl (methylscopolamine nitrate) was observed in four cases; in all cases, inhibition of the vagal system produced an accelerated auricular rate and clearing of the sinus arrhythmia. In one of the four cases there was also a pronounced increase in the ventricular rate. When amyl nitrite was given by inhalation in two cases, the auricular rate was much increased in both of them, the sinus rhythm was regularized and in one the ventricular rate was almost doubled. The author concludes that the sinus arrhythmia in complete A-V block is not associated with a fixed range of rate but is probably the result of a particular state of vegetative tone. Adrenaline was given intravenously in two cases. The sinus arrhythmia present before the injection cleared in about 30 seconds but 1 to 1½ minutes after the injection it had returned and was even more pronounced even though the auricular rate was higher than the control level. It is felt from this that the sinus arrhythmia is not linked to a certain low auricular rate. In one of the cases studied, ectopic auricular contractions with negative P waves occurring immediately after a QRS complex were observed.

ROSENBAUM

PATHOLOGY

Rabiner, S. F., Specter, L. S., Repstein, C. B. and Schlecker, A. A.: Chronic Constrictive Pericarditis As A Sequel to Acute Benign Pericarditis. New England J. Med. **251:** 425–428 (Sept. 9), 1954.

A case of acute pericarditis occurring in a man aged 40 years is described in detail. The initial symptoms consisted of substernal pressure, dyspnea and fever. There was no antecedent respiratory infection and no pain in the chest. Massive pericardial effusion and elevation of the venous pressure marked the clinical course. The electrocardiograms showed only small deflections in all leads and slight right axis deviation. Three pericardial paracenteses were done. A pericardiectomy was performed 3 months after the onset. A thickened whitish visceral pericardium was found with limitation of the excursion of both ventricles. The epicardium was stripped as a thin fibromembranous sheet from the right atrium, the great veins and the anterior, posterior and inferior surfaces of the right and left ventricles. Microscopic study disclosed granulation and loose and dense connective tissues with considerable discrete and coalesced mononuclear-cell infiltrations. Operation was followed by clinical improvement although the heart was still slightly enlarged 18 months postoperatively. This case is considered by the authors to demonstrate a possible etiologic relationship between acute benign pericarditis and chronic constrictive pericarditis.

ROSENBAUM

PHARMACOLOGY

MacCanon, D. M. and Horvath, Steven M.: Some Effects of Serotonin in Pentobarbital Anesthetized Dogs. Am. J. Physiol. **179:** 131 (Oct.), 1954.

When Serotonin creatinine sulfate was administered into the pulmonary artery an uncomplicated rise in pressure was observed in both greater and lesser circulations. This was followed by an increased output. In most cases a bradycardia with electrocardiographic changes and a bout of hyperpnea followed by apnea were the findings. The vacular and respiratory effects occurred almost simultaneously. This suggests a nervous factor.

OPPENHEIMER

Mendeloff, A. I.: Effect of Intravenous Infusions of Ethanol upon Estimated Hepatic Blood Flow in Man. J. Clin. Invest. **33:** 1298 (Oct.), 1954.

An intravenous infusion of 5 per cent alcohol in saline was administered five subjects with peptic ulcer. The hepatic blood flow was measured by the hepatic vein catheterization and bromsulfalein (BSP) technic. Under the conditions of this study there was a significant increase in hepatic blood flow over values obtained after saline alone. These findings can best be explained as due to a lowering of the peripheral resistance of the splanchnic vascular bed.

Other evidence obtained showed no subjective effects from the rather small dose used. There was minimal peripheral disappearance of alcohol, most subjects showing significant hepatic uptake. The findings are also in agreement with current concepts of the conversion of alcohol to acetaldehyde.

WAIFE

Daley, J. W.: Diuretic Effect and Local Tolerance of a New Type of Mercurial Rectal Suppository: A Preliminary Report. Am. J. M. Sc. **228:** 440 (Oct.), 1954.

Mercaptomerin sodium in doses of 0.5 Gm. (165 mg. mercury equivalent) was incorporated into a cocoa butter suppository for administration to edematous patients in order to evaluate the diuretic effect of the drug given by the rectal route. The suppository was shown to have no local irritating effects in animals or in human subjects. Thirteen outpatients received a suppository every second night for periods up to 6 months with the exception of brief control intervals during which no diuretic was given. Twelve hospital patients were treated with suppositories nightly for one to two weeks. The diuretic response was judged as adequate in 85

per cent of outpatients and in 75 per cent of the hospitalized group. Patients receiving cortisone who showed a tendency to salt retention were controlled satisfactorily by the Thiomerin suppository. The author states that the rectal administration of the diuretic will maintain some patients in an edema-free state while, in others, injection will be required at less frequent intervals.

SHUMAN

Poe, M. F.: The Use of Aramine as a Pressor Agent During Spinal Anesthesia. Anesthesiology **15:** 547 (Sept.), 1954.

In 240 unselected cases, Aramine, a sympathomimetic amine chemically related to Propadrine, was employed as a vasopressor agent to maintain the blood pressure during spinal analgesia. The pressor effect appeared about 15 minutes after subcutaneous administration of 3 to 5 mg. and one to two minutes after the intravenous administration of 1 mg. The effect lasted up to one hour. The action of the drug was compared with that of Methoxamine and ephedrine which were used as vasopressor agents in similar groups of patients. The three drugs were equipotent vasopressor agents, prophylactically as well as therapeutically. Aramine had the shortest duration of pressor effect and Methoxamine the longest. Following Aramine and Methoxamine, bradycardia and increased pulse pressure were commonly observed. Neither Aramine nor ephedrine was associated with any complications, but hypertension occasionally was observed late after the use of Methoxamine. The author concludes that Aramine appears to be a safe vasopressor drug for subcutaneous and intravenous administration.

SAGALL

Wool, I. G., Goldstein, M. S., Ramey, E. R. and Levine, R.: Role of Epinephrine in the Physiology of Fat Mobilization. Am. J. Physiol. **178:** 427 (Sept.), 1954.

When female rats are fasted and then fed ethionine they develop fatty livers. This result is prevented by prior adrenalectomy. Large doses of cortisone do not correct this. However, when small amounts of cortisone are combined with epinephrine the ability to mobilize fat is restored. Fat mobilization was also reduced by ergotamine and adrenal demedullation to levels resembling those in total adrenalectomized rats. The ability to develop a fatty liver in the demedullated rats was restored by epinephrine. The autonomic nervous system and the closely related adrenal medulla have important roles in fat metabolism.

OPPENHEIMER

Muirhead, Ernest E., Goth, Andres and Jones, Frances: Sodium and Potassium Exchanges Associated with Nor-Epinephrine Infusions. Am. J. Physiol. **179:** 1 (Oct.), 1954.

Nor-epinephrine infusions were carried out in dogs for periods of 20 to 50 minutes. The dose was 1 to 7 mg./Kg. This produced a marked hypertension. Plasma sodium was depressed and that of potassium elevated. Chloride changes were not significant.

OPPENHEIMER

Rapaport, S. J., Aas, K. and Owen, P. A.: The Lipid Inhibitor of Brain: Mechanism of Its Anticoagulant Action and Its Comparison with the Soy Bean Inositol Phosphatide Inhibitor. J. Lab. & Clin. Med. **44:** 364 (Sept.), 1954.

A series of experiments is presented to define the mechanism of action of the lipid inhibitor in human brain cephalin preparations and to compare its activity with that of a preparation of soy bean inositol phosphatide inhibitor. It was found that the lipid inhibitor blocks the reaction between tissue thromboplastin and proconvertin to form convertin. It is ineffective in the presence of preformed convertin and in this respect differs from the soy bean inositol phosphatide inhibitor which remains active in presence of preformed convertin.

HARVEY

Moyer, J. H., Snyder, H., Miller, S. I. and Smith, C. P.: Cerebral Hemodynamic Response to Blood Pressure Reduction with Phenoxybenzamine (Dibenzyline-688A). Am. J. M. Sc. **228:** 563 (Nov.), 1954.

Lowering of the blood pressure of hypertensives results in a compensatory dilatation of the cerebral arterioles with maintenance of cerebral blood flow. The present study was conducted to determine whether an adrenergic blocking agent (Dibenzyline) may influence the vasoconstrictor tone of the cerebral vessels, although it is generally conceded that the sympathetic system does not directly regulate cerebral blood flow because of negative effects following stellate ganglionic blockade. Cerebral blood flow was determined by the nitrous oxide procedure in 7 patients with severe hypertension. Following control observations the drug was administered intravenously and further observations were made on cerebral hemodynamics. With moderate reductions of blood pressure, the cerebral blood flow and oxygen consumption were not affected. With the development of low normotensive ranges cerebral blood flow was depressed. However, there was an increase in oxygen extraction from the blood flowing through the brain so that cerebral anoxia was avoided. It appears that the adrenergic blocking agents affect the cerebral vessels of hypertensive patients in the same way other hypotensive agents do. There is no evidence of preferential release of cerebral vasoconstriction following Dibenzyline administration.

SHUMAN

Bacchus, H.: Influence of Epinephrine on the Plasma Content of 17-Hydroxycorticosteroids. Am. J. Physiol. **178:** 437 (Sept.), 1954.

Epinephrine does not alter the level of circulating corticosteroids in adrenalectomized rats given cortisone or intact rats which have received ACTH. Epinephrine and ACTH do not significantly alter the "in vitro" metabolism of liver slices on the cortisone side chain or conjugated unsaturated system of the nucleus. Circulating 17-hydroxycorticosteroids were not increased in normal rats when epinephrine was injected but ACTH produced an observed large increase which was significant.

OPPENHEIMER

Feldman, L., Schaefer, G. L., Goldstein, S. E. and Forman, I. M.: Bishydroxycoumarin (Dicumarol) Therapy in Myocardial Infarction. Arch. of Int. Med. **94:** 433 (Sept.), 1954.

The records of 300 patients with acute myocardial infarction, 150 receiving no anticoagulants, are evaluated. There were seven thromboembolic complications in the group not receiving bishydroxycoumarin (Dicumarol) and six in the group under therapy with the anticoagulant. There were three minor bleeding episodes. In only 29.33 per cent receiving bishydroxycoumarin, was the prothrombin level maintained under 40 per cent of the control prothrombin activity. The authors believe that anticoagulant drugs should not be used routinely in patients with acute myocardial infarction.

BERNSTEIN

Sarnoff, S., J. and Cope, O.: The Effect of Atropine and Scopolamine on the Subsequent Injection of Epinephrine in Thyrotoxic and Euthyroid Patients. Anesthesiology **15:** 484 (Sept.), 1954.

In a series of euthyroid and thyrotoxic patients it was found that the effect of epinephrine hydrochloride was potentiated by the preliminary injection of atropine sulfate. This was evidenced by a higher and more prolonged increase in pulse rate or systolic blood pressure and in the thyrotoxic patient by an augmentation of subjective distress and muscular tremor. Scopolamine may also augment the effects of epinephrine, but did so less often and to a lesser degree than atropine. Since it also is effective as a drying agent, the authors conclude that when such premedication is indicated in the thyrotoxic patient scopolamine would be preferable to atropine.

SAGALL

Sherry, S., Titchener, A., Gottesman, L., Wasserman, P. and Troll, W.: The Enzymatic Dissolution of Experimental Arterial Thrombi in the Dog by Trypsin, Chymotrypsin and Plasminogen Activators. J. Clin. Invest. **33:** 1303, (Oct.), 1954.

Studies are in progress in various laboratories regarding the dissolution of intravascular thrombi and emboli by the direct introduction of proteolytic enzymes (trypsin) or activation of the host's plasminogen (streptokinase). In this study experimental arterial thromboses were produced in the femoral artery of dogs by local injection of thromboplastin.

Ten per cent of the clots disappeared spontaneously. Infusion of trypsin was not associated with an increase in dissolved clots, although there were significant changes in the prothrombin and fibrinogen content of the blood. Chymotrypsin restored the circulation in about half the thrombosed vessels. The mechanism of this effect is not known.

Streptokinase alone, or with partially purified human plasminogen, also dissolved about 50 per cent of the clots.

WAIFE

Mirkin, Bernard L., and Bonnycastle, Desmond D.: A Pharmacological and Chemical Study of Humoral Mediators in the Sympathetic Nervous System. Am. J. Physiol. **178:** 529 (Sept.), 1954.

Postganglionic fibers supplied to liver, spleen and intestine released over 90 per cent norepinephrine when stimulated electrically. The norepinephrine:epinephrine ratio obtained from outflowing venous adrenal medullary blood was not correlated with the proportion of these substances released upon adrenergic nerve stimulation. It is pointed out that one can not predict the nature of adrenergic mediating substances throughout the body by merely determining the norepinephrine:epinephrine ratio in outflowing venous adrenal medullary blood.

OPPENHEIMER

Van Bergen, F. H., Buckley, J. J., French, L. A., Dobbin, A. B., and Brown, I. A.: Physiologic Alterations Associated with Hexamethonium-induced Hypotension. Anesthesiology **15:** 507 (Sept.), 1954.

Various studies were performed in fourteen anesthetized human subjects after hypotension had been induced by the intravenous administration of Hexamethonium. The magnitude of the fall in blood pressure was influenced by the dose of the drug. The maximal level was attained with the initial dose of 25 to 50 mg. and additional amounts just prolonged the effects without producing a further fall in blood pressure. The maintenance of hypotension was potentiated by an adequate plane of anesthesia. Fowler's position and increased vascular tonus predisposed to the more precipitous falls in arterial blood pressure.

In patients under hexamethonium blockade the vasopressor overshoot reflex following Valsalva's maneuver and postural change was abolished, and the normal reflex cardiovascular responses to hypercarbia and hypoxia were eliminated. An altered response to peripherally acting vasopressor drugs was also found.

Studies of certain secondary effects of hexamethonium revealed that an increase in circulation

time, a decrease in the ear capillary oxygen saturation, and an increase in the cerebral arterio-venous oxygen difference accompanied moderate to severe hypotension. With marked hypotension and Fowler's position electrocardiograms and electrocorticograms revealed changes indicative of hypoxia of the heart and of the brain. These findings suggest that with hexamethonium in anesthetized patients there is a reduction of the cerebral and coronary blood flow and also a decreased cardiac output. The production and maintenance of hypotensive anesthesia thus can be dangerous since the capacity of the blood reservoir may exceed the blood volume and the brain may be rendered completely ischemic by placing the patient in a steep Fowler's position.

SAGALL

PHYSICAL SIGNS

Leatham, A.: Splitting of the First and Second Heart Sounds. Lancet **2:** 607 (Sept. 25), 1954.

Slight splitting of both heart sounds is audible in most normal subjects. The first sound splitting is most obvious in the tricuspid and mitral areas, especially the former, and during expiration. The first component is usually of mitral origin and the second of tricuspid. Right bundle branch block may exaggerate the splitting; left bundle branch block may obliterate it; mitral stenosis with delay in closure of the mitral valve may reverse the order of the two components. Splitting of the first sound heard at the base should suggest bundle branch block or the early systolic click of a dilated pulmonary artery or aorta.

Splitting of the second pulmonary sound during inspiration occurs in many normal persons. The first component is of aortic origin and the second of pulmonary origin. The first component is synchronous with the "second sound" heard in the aortic and mitral areas. The pulmonary closure sound is usually not audible at the apex unless it is greatly intensified as a result of pulmonary hypertension. The exception is interatrial septal defect with normal pulmonary pressure but dilated right ventricle in which case both components of the split second sound may be audible at the apex. Pronounced splitting of second sound suggests bundle branch block or interatrial septal defect. In the latter condition pulmonary valve closure is delayed because of the marked increase in right ventricular blood flow as compared with the left. The presence or absence of a delay in the pulmonary component of the second pulmonary sound can give useful information in tetralogy of Fallot.

The opening mitral snap of mitral stenosis can be distinguished from a split second pulmonary sound by the fact that the opening snap is heard best in expiration. It is true that right bundle branch block and pulmonary hypertension with delay of an accentuated second pulmonary component may be confusing. One can be certain if one hears all three sounds: aortic closure, pulmonary closure, mitral opening snap. A third heart sound occurs later than an opening mitral snap and is to be distinguished from it since with mitral valve disease the first suggests predominant mitral regurgitation and the second, predominant mitral stenosis.

MCKUSICK

PHYSIOLOGY

Koster, L., Alers, C. J., Van Ham, E. H. and Van Westreenen, E.: Reactions to Heavy Physical Exertion and Thorn Tests in the Analysis of Physical Insufficiency Syndromes. Acta med. Scandinav. **150:** 63–79 (Nov. 9), 1954.

These authors used a pack test to observe the circulatory and hematological responses to heavy physical exertion in normal persons, a group of 31 patients with bronchial asthma and 30 vasolabile young men. In the vasolabile persons in whom the effort test caused a collapse or pre-collapse, there was an eosinopenic response far beyond that of normal or asthmatic patients. This is considered to mean that the adrenal reaction to the same stimulus must be much greater in vasolabile than in healthy or asthmatic individuals. In the studies of the asthmatic patients it was observed that the injection of Insulin was capable of increasing the total leucocyte count to a much higher degree than did the administration of Adrenaline.

ROSENBAUM

Hubay, C. A., Waltz, R. C., Brecker, G. A., Praglin, J., and Hingson, R. A.: Circulatory Dynamics of Venous Return During Positive-Negative Pressure Respiration. Anesthesiology **15:** 445 (Sept.), 1954.

The authors studied the blood flow in the superior vena cava in experimental animals by direct measurement with a low-resistance electrically recording steam-bristle flowmeter. The purpose of the study was to evaluate the circulatory effects of an experimental positive-negative pressure respirator.

In the closed chest, the addition of negative pressure to the respiratory cycle increased the venous return significantly. This is physiological since the mechanisms of increased venous return correspond to those observed with spontaneous inspiration. In the closed chest, positive pressure lung inflation has a detrimental effect reducing the rate of venous return and diminishing the inflow in the right side of the heart. Intermittent positive-negative pressure respiration increased the venous return over that measured during positive-atmospheric pressure respiration. The authors conclude on the bases of these experiments that intermittent positive pressure respirations with a clinical respirator in the closed chest increased venous return significantly over that measured during positive-atmospheric pressure respiration.

To study the influences of positive-negative pres-

sure respiration on the impaired circulation a hypovolemic state was created by bleeding the animals until the arterial blood pressure was reduced to about 50 mm. In these animals, intermittent positive-atmospheric pressure respiration slowed venous return but intermittent positive-negative respiration increased venous return relatively more than in the state of normovolemia.

In the open chest, positive pressure lung inflation impeded venous return. The interposition of a negative phase between positive pressure lung inflation did not benefit the circulation. This confirms the belief that the mechanism responsible for the increased venous return during positive-negative pressure respiration is thoracic aspiration. Opening the chest abolishes this factor.

SAGALL

Rosenfeld, S., Sellers, A. L., Marmorston, J. and Eliasch, H.: Effect of Renin on Renal Function. Am. J. Physiol. **179:** 177 (Oct.), 1954.

In the rabbit maximal tubular secretion of PAH is observed at plasma levels of 25 to 30 mg. per 100 cc. This tubular transport is not changed by renin even though a marked diuresis and protein-uria result. Also, renin does not affect creatinine clearance. If para-amino hyppurate in plasma increases from 10 to 15 mg. per cent up to 30 to 60 mg. per 100 cc., creatinine clearance decreases.

OPPENHEIMER

Leaf, A., Kerr, W. S. Jr., Wrong, O. and Chatillon, J. Y.: Effect of Graded Compression of the Renal Artery on Water and Solute Excretion. Am. J. Physiol. **179:** 191 (Oct.), 1954.

Renal arteries were compressed while the urine being produced was dilute. Under these circumstances the concentration of urine was unchanged. There was, however, a decrease in the urine volume. Total solute excreted was reduced in proportion to the decrease in glomerular filtration rate. On the other hand, if the renal artery was constricted during production of a concentrated urine there was some decrease in concentration and flow. Rate of total solute excretion was still proportional to the reduced glomerular filtration rate. The authors stress the fact that acute reductions in renal blood flow under the conditions of these experiments do not produce increased concentration of urine.

OPPENHEIMER

Burwell, C. S.: Circulatory Adjustments to Pregnancy. Bull. Johns Hopkins Hosp. **95:** 115 (Sept.), 1954.

The uterus and its contents account for 70–80 per cent of the increased oxygen consumption (raised about 20 per cent above the non-pregnant level), increased work of the maternal heart accounts for some of the rest. Pulse rate rises to a maximum at about eight months and declines somewhat thereafter. Systolic blood pressure changes little; the diastolic declines slightly. Cardiac output rises to a maximum of 40 to 50 per cent above the non-pregnant level at 32 weeks and declines thereafter. Plasma volume rises to a maximum at about eight months declining thereafter. Red cell mass also increases but not in proportion to plasma volume; furthermore, it continues to increase until the end of pregnancy. There is evidence that the leg veins and the pulmonary vasculature are repositories for some of the increased blood volume. Minute lung ventilation is elevated out of proportion to oxygen consumption. Pregnancy does not decrease vital capacity which is maintained at the expense of residual lung volume. The lung in pregnant women is in a relatively expiratory position like that of obesity and pneumoperitoneum. Breathing from this partially deflated position may require more effort and this may be one factor in the unpleasant consciousness of breathing called dyspnea of pregnancy. Slowing of the heart rate occurs during that phase of uterine contraction when placental blood flow is reduced—a phenomenon comparable to Branham's sign of peripheral arteriovenous fistula.

MCKUSICK

Berneus, B., Carlsten, A., Holmgren, A. and Seldinger, S. I.: Percutaneous Catheterization of Peripheral Arteries as a Method for Blood Sampling. Scandinav. J. Lab. & Clin. Invest. **6:** 217–221 (No. 3), (July 15), 1954.

A technique for percutaneous catheterization of peripheral arteries employing a polyethylene catheter is described in detail. The procedure has been used in a variety of applications in about 500 patients by these authors. The catheter has been left in situ for as long as two weeks in some instances. When left in place for long periods the catheter must be flushed with heparine solution at least four times daily and after each blood sample. The most common complications are hematomata and spasm in the artery. These complications are rarely great enough to interfere with application of the procedure. The brachial artery was found most suitable for puncturing. The femoral artery should be avoided in ambulant patients, especially elderly individuals. This technique eliminates the need for frequent punctures, reduces the feeling of immobilization and the tendency to hyperventilation and makes for a more tranquil patient.

ROSENBAUM

RHEUMATIC FEVER, RHEUMATIC HEART DISEASE, COLLAGEN DISEASES

Chamovitz, R., Catanzaro, F. J., Stetson, C. A. and Rammelkamp, C. H., Jr.: Prevention of Rheumatic Fever by Treatment of Previous Streptococcal Infections. I. Evaluation of Benzathine Penicillin G. New England J. Med. **251:** 466–471 (Sept. 16), 1954.

The value of a single intramuscular injection of

dibenzylethylenediamine (DBED) dipenicillin G in the prevention of rheumatic fever was determined by comparing results of treatment of 257 patients with exudative pharyngitis by this means with 109 untreated control patients. In the control group two patients developed definite rheumatic fever and one developed nephritis. These complications did not occur in the treated group although six patients developed multiple joint symptoms or signs, three had urticaria, one had pruritis, and one had prolongation of atrioventricular conduction. These manifestations were considered toxic reactions to the penicillin. The treatment was effective in that only one of 195 throat cultures was positive for organisms of the infecting type after a three-week interval in the treated group whereas cultures were positive in 80 per cent of the control group at this same interval. A single injection of DBED penicillin appeared more effective than three injections of procaine penicillin G containing two per cent aluminum monostearate given every other day. There was a distinct inhibition of antistreptolysin formation in the treated group. In most patients there was discomfort at the site of intramuscular injection of the DBED penicillin for 24 to 48 hours. Until the frequency of reactions is established a single intramuscular dose of 600,000 or possibly 900,000 units of DBED penicillin is recommended for streptococcal infections to prevent rheumatic complications.

ROSENBAUM

Landing, B. H., and Feriozi, D.: Effect of ACTH on the Adrenals in the Nephrotic Syndrome and Rheumatic Fever. J. Clin. Endocrinol. **14:** 1023 (Sept.), 1954.

The effects of ACTH on the adrenals of small groups of patients with the nephrotic syndrome due to chronic glomerulonephritis and with rheumatic fever were presented. The adrenals of control untreated patients with the nephrotic syndrome had a smaller average weight and a higher fat content than those of untreated patients who had rheumatic fever or leukemia. In the one nephrotic patient who died while being treated with ACTH, all three zones of the adrenal cortex showed a decrease in fat and an increase in zone thickness and cell size, the response of the zona glomerulosa being similar to that seen in leukemic patients treated with cortisone before receiving ACTH. The findings in the patients with rheumatic fever support those seen in patients with leukemia, namely, that the zona fasciculata is more responsive to ACTH than is the zona reticularis, and that cortisone alters the morphologic response of the adrenal cortex to ACTH.

MAXWELL

Saldanha, A., Moniz de Bettencourt, J. Madeira P. P., Schreck, M. and Barreto Fragoso, J. C.: The Electrokymogram of the Left Atrium, in Normal and Pathologic Conditions, in Particular in Mitral Disease. Cardiologia **25:** 212 (Fasc. 4), (Oct.), 1954.

The authors analyzed electrokymograms of the left atrium in the right anterior oblique diameter in 15 normal and 80 cardiac patients, 70 of which had mitral valvular disease. Three types of left atrial kymograms were found. Type I, corresponding to the normal curve of most of the previous descriptions was characterized by two to three positive waves (a, c, v) with presystolic and systolic phases of collapse. In type II, which is termed the ascending type, the systolic collapse is replaced by a slowly ascending line. Type III is typified by a systolic plateau. A Valsalva test sometimes changes type II to III.

The significance and mode of origin of the various types are discussed. In cardiac patients without mitral valvular disease tracing of type I and II were generally found. Plateau tracings (III) were encountered most frequently in mitral disease with auricular fibrillation, a large left atrium and elevated pulmonary wedge pressure, but it can also be found in pure mitral stenosis and in other cardiopathies with auricular fibrillation, in the absence of mitral regurgitation.

PICK

Hebbert, F. J. and Rankin, J.: Mitral Valve Disease over the Age of 50. Acta med. scandinav. **150:** 101–118 (Fasc. 2) (Aug.), 1954.

The authors report that of all the cases of mitral stenosis observed at their clinic over a five year period, 15 per cent were over the age of 50 years when first diagnosed. This report is concerned with 106 patients with mitral stenosis, all of them over age 50. The diagnosis was made or confirmed at post mortem examination in 57, 13 died without permission for autopsy and 36 were living at the time of the report. Of the 57 patients who died, death was directly attributable to the heart in 38. Congestive cardiac failure was present in 34 cases and when mitral stenosis was the sole valvular lesion present congestive failure was almost invariably associated with auricular fibrillation. Systemic emboli were found in 30 patients, eight of whom had bacterial endocarditis. In the 57 autopsied cases the mitral stenosis was severe, i.e. "buttonhole" or "slit-like" in 29 patients, ball thrombi were present in the left auricle in two cases, in eight there was no cardiac enlargement, at times despite tight mitral stenosis, and in no case was there a grossly dilated left auricle. A history of rheumatic fever was obtained in 48.7 per cent of the patients. There were 71 women in the series; of the 45 in whom an adequate obstetrical history could be obtained, 39 had borne children, the total number being 157, the average per mother, 4. One woman who died of subacute bacterial endocarditis at age 51 had 12 children. Congestive cardiac failure occurred at some

time in 58 per cent of the patients, usually precipitated by auricular fibrillation or other cardiovascular lesions. Fourteen patients had pain of myocardial ischemic type although in several of them there were serious cardiovascular disorders in addition to the mitral valvular disease. In 31 cases the diagnosis of mitral valvular disease was made only at post mortem examination. The subsidiary physical signs which are believed to be suggestive of mitral stenosis in this group of individuals include a loud first heart sound, an accentuated pulmonary second sound, a malar flush and a third heart sound. Isolated mitral stenosis was present in 40 of the 57 cases examined at autopsy.

The authors suggest that longevity in patients with mitral stenosis may result from acquisition of the rheumatic infection late in life or infrequency of recurrences of rheumatic activity after the development of definite valvular sclerosis. The authors express the opinion, based upon the experience with long survivals despite undisputable mitral stenosis, that commissurotomy should be confined to patients who are actually disabled by the condition. The diagnosis of mitral stenosis should be suspected in elderly patients with a lengthy history of mild cardiac disability or a prolonged history of pulmonary complaints.

ROSENBAUM

Rodbard, S., and Williams, F.: The Dynamics of Mitral Insufficiency. Am. Heart J. **48:** 521 (Oct.), 1954.

The basic model for this study consisted essentially of a balloon-like ventricle which filled by gravity from a reservoir during diastole. The ventricle consisted of either an inelastic bag of dried sheep cecum, or of a latex rubber condom. The parchment was used in studies requiring a constant and diastolic pressure. Latex was used to permit varying degrees of filling depending on atrial pressure or on duration of diastole. Compressed-air valves providing energy to ventricular contraction were adjusted to accomplish emptying of the ventricle in each beat. During ventricular systole the ejected blood could pass in this arrangement through a "mitral" valve into the atrium, or through the "aortic" valve into the aortic chamber.

After analysis of the hemodynamic factors, it was learned that forward flow into the aorta was enhanced by increases in atrial pressure, ventricular filling, viscosity of the blood, celerity of ventricular contraction and by lateral pressure effects on the regurgitation orifice. The tendency to mitral regurgitation is heightened by a rise in systemic arterial pressure, an increase in the size of the regurgitation orifice, or a decrease in the celerity of ventricular contraction. The proximity of the aortic orifice to the mitral opening operates to reduce reflux because of competition of the two valves for streamlines of flow.

The significance of those experimental findings are related by the author to clinical mitral insufficiency.

RINZLER

Mitchell, A. M., Sackett, C. H., Hunzicker, W. J. and Levine, S. A.: The Clinical Features of Aortic Stenosis. Am. Heart J. **48:** 684 (Nov.), 1954.

This study is a review of 533 patients with aortic stenosis. These consisted of 214 examined postmortem, 158 diagnosed by the detection of a calcified aortic valve on fluoroscopy, and 161 as determined by customary clinical criteria. The patients were divided into four major groups, i.e., pure aortic stenosis (131 cases), aortic stenosis with insufficiency (244 cases), aortic and mitral stenosis with or without associated incompetence (149 cases), and stenosis of the aortic, mitral, and tricuspid valves with or without accompanying insufficiency (29 cases). Evidence was presented to indicate that the vast majority of patients with aortic stenosis are primarily rheumatic in origin even when of the calcific type. The life expectancy and the age at death have been influenced by the recent improvement in the care of cardiac patients. The average age at death of 326 known fatal cases in this study was 52.2 years. For pure aortic stenosis the average age was 65.3 years, for aortic stenosis and insufficiency it was 52.5 years, for aortic and mitral stenosis 48.4 years, and for trivalvular stenosis 36.5 years. The average duration of life after the onset of congestive failure was 42.5 months; 22.7 months for pure aortic stenosis; 28.9 months for aortic stenosis and insufficiency; 56.4 months for aortic and mitral stenosis; and 80.0 months for trivalvular stenosis. Angina pectoris was present in 159 cases of 29.8 per cent of the entire 533 cases. Syncopal attacks occurred in at least 12.6 per cent of the series. Sudden death occurred in 40 instances (23.4 per cent) where the mode of death was known, excluding subacute bacterial endocarditis. Some form of conduction disturbance was present in 26 per cent of the 455 cases in whom tracings were available. Auricular fibrillation was present in 10 per cent of those with aortic stenosis alone and in 55 per cent of those who also had mitral stenosis. Among 127 patients in whom the electrocardiograms were adequate for the detection of left ventricular hypertrophy, it was found to be present in 74.8 per cent of the cases. In those with aortic stenosis without mitral stenosis, this figure was 84 per cent. The average blood pressure for 203 cases examined post-mortem was 133/70 mm. Hg with a range of 85 mm. to 240 mm. systolic and zero to 165 mm. diastolic.

The most constant finding in these cases was the presence of a systolic murmur. The presence or absence of a systolic thrill was directly related to the loudness of the murmur. It was practically never

palpable unless the murmur was of Grade 3 and generally of grade 4 intensity or louder. The aortic second sound was decreased or absent in the majority of the cases or aortic stenosis without mitral stenosis but there were numerous instances in which the sound was normal or increased, especially if hypertension were present. A forceful or lifting apex impulse proved to be a valuable indication of left ventricular hypertrophy. Subacute bacterial endocarditis was found in 10 per cent of this series. The most valuable roentgenologic finding was the detection of a calcified aortic valve. The average heart weight was 606 grams for pure aortic stenosis, 686 Gm. for aortic stenosis and insufficiency, 593 Gm. for aortic and mitral stenosis, and 543 grams for trivalvular stenosis. In general, it can be concluded that the diagnosis of aortic stenosis can be made with a high degree of accuracy. Considerable variation was found in the clinical progress of the disease. Finally, a prediction of the degree of stenosis could be made with only a moderate degree of accuracy.

RINZLER

Boas, E. P., Elster, S. K. and Adlersberg, D.: Calcific Aortic Stenosis: Study of Serum Cholesterol. Am. Heart J. **48:** 485 (Oct.), 1954.

The serum cholesterol of 86 patients with aortic stenosis, 43 men and 43 women, and of sixty-seven patients with chronic rheumatic valvular, 22 men and 45 women, was determined. The criteria for the diagnosis of aortic stenosis was as follows: a systolic thrill accompanied by a harsh systolic murmur at the aortic area; a grade 4 to 6 harsh systolic murmur at the aortic area; a grade 4 to 6 systolic murmur audible all over the precordium, even if loudest at the apex. An accompanying diastolic murmur or a history of syncope or of angina pectoris fortified the diagnosis.

Two standards were used to determine whether the patients were hypercholesteremic. Using Ancel Keys' standards, 48.8 per cent of the females and 18.6 per cent of the males with aortic stenosis were hypercholesteremic, whereas of those with chronic rheumatic valvular disease 13.3 per cent of the females and 13.6 per cent of the males were hypercholesteremic. By using standards derived from a study of a random sample of a union population in New York City, 53.5 per cent of the females and 27.9 per cent of the males with aortic stenosis were hypercholesteremic; and of those with rheumatic valvular disease 20 per cent of the women and 18.2 per cent of the men were hypercholesteremic.

Of the patients with aortic stenosis 70 per cent apparently had had previous rheumatic infection. These results favor the hypothesis that in persons with hypercholesteremia aortic stenosis may be caused by atherosclerosis of a normal aortic valve, but that in most instances it is caused by a secondary atherosclerosis implanted on aortic cusps scarred by ancient rheumatic infection.

RINZLER

ROENTGENOLOGY

Carmichael, J. H. E., Julian, D. G. and Jones G. P.: Radiological Signs in Pulmonary Hypertension. Brit. J. Radiol. **27:** 393 (July), 1954.

This article suggests that the presence of small horizontal lines, about one inch long, seen near the costophrenic angles, and termed "Lines B of Kerley" are frequently present in roentgenograms of patients with pulmonary hypertension secondary to mitral stenosis. Such lines were most often present when mean pulmonary artery pressures were 39 mm. of mercury or higher.

SCHWEDEL

Kjellberg, S. R. and Olsson, S. E.: Roentgenologic Studies of the Sphincter Mechanism of the Caval and Pulmonary Veins. Acta Radiol. **41:** 481 (June), 1954.

Superior and inferior vena cavae and the pulmonary veins were studied by angiocardiography and selective angiography in 10 children and in six dogs. During atrial systole sphincter like narrowing was observed distal to the atria, while in atrial diastole these areas were observed to widen.

The sphincteric sites correspond to the circular fibres present anatomically and are considered by the authors as functionally significant in preventing reflux of blood during atrial systole. In this way flow from the atria to the ventricles is facilitated, the flow of blood into the atria during atrial diastole thus is partially regulated.

SCHWEDEL

BOOK REVIEWS

Hypertension and Nephritis. *A. M. Fishberg*, Ed. 5, Philadelphia. Lea and Febiger, 1954. 986 pages, 49 figures. Price $12.50.

This book has an established place in medical literature. The first edition was immediately popular and each successive edition has been used as a reference by student, teacher and clinician. The present edition will continue this justly deserved reputation. Although the format of the book has remained unchanged, each section has been throughly revised to present the present day concepts of hypertension and nephritis. After a brief review of normal renal physiology and impaired renal function, the author discusses clinical syndromes of azotemia, uremia and edema. There is a chapter on renal function tests. With this basic background specific diseases are discussed in the conventional manner. The order of presentation in this section could be improved inasmuch as it begins with a few chapters on arterial hypertension, including an excellent one on pathogenesis, and then has several chapters on specific renal diseases only to return to more chapters on essential hypertension. It seems that essential hypertention could follow arterial hypertension with some economy in length without sacrificing detail.

A review of the five editions of this book is an historical review of the field of hypertension and kidney disease in the last 30 years as well as an evaluation of the development of an individual. Doctor Fishberg has always incorporated the latest concepts in each edition and flavored them with personal opinions about their importance and clinical significance. As an example, the second edition of this book in 1931 introduced a discussion of pheochromocytoma as well as the role of the carotid sinus in regulation of blood pressure as recent advances. Today these subjects are familiar to all. In previous editions the author has stated that urea clearance test as a measure of renal function was not of much value. The present edition says that it is a "splendid means for estimating the severity and following the course of impairment of renal function." In the treatment of essential hypertension the present edition contains a short review of all the new hypotensive agents whereas in previous editions treatment was confined to sedatives and general measures such as vacations, mental hygiene, diet, etc. As the author states, the most significant change in 30 years is the changing concept of the level of blood pressure which is pathological. The second edition states that a pressure of over 150 systolic or 100 diastolic is always pathological. The third edition raises some question about this and the present edition says that when these levels are exceeded one should think of the possibility of hypertension.

The 15 years since the last edition of this book have been fruitful and the author has accurately recorded them. Each chapter is a thorough discussion of the subject followed by a good bibliography to allow the reader further exploration. The discussion on diabetic glomerulosclerosis and the chapter on the importance of chronic pyelonephritis are worthwhile additions. The praise given all the former editions holds for the present one.

JEROME M. WALDRON, M.D.

Ciba Foundation Symposium on Hypertension-Humoral and Neurogenic Factors. *G. E. W. Wolstenholme, and M. P. Cameron, Editors, Assisted by J. Etherington.* Boston. Little, Brown and Co., 1954. 294 pages, 73 figures. Price $6.75.

This symposium on hypertension continues the same high quality of presentation and discussion of previous Ciba symposia. The list of participants includes most of the familiar names in hypertensive research in this country, England and Europe. After a few introductory remarks by Doctor Pickering, 21 papers are presented on most phases of research on the neural and humoral mechanisms of hypertension. The discussion of each paper, although not detailed, is often pointed and raises some questions and some doubts. Although the concept of neural mechanisms pervades the whole symposium only four papers are specifically concerned with this phase. Humoral mechanisms are stressed primarily. This usually means the renin mechanism, but in this book the renin production by the kidney is given second place to the concept that the kidney may actually destroy a pressor substance. Hypertension would therefore be a loss of this faculty of the kidney. It is interesting that five of the papers are concerned with salt and water metabolism in hypertension.

As a resume of contemporary thought on the etiology and mechanism of hypertension the book is excellent. Some papers can be read by the novice with understanding. Other papers will not be comprehended without some background. Each paper has a bibliography but the articles quoted are not the review type which would orient an unfamiliar reader. In addition, many of the references are in the foreign literature which would not be available to the casual reader. For these reasons the book is not recommended for the casual reader or for the physician who is interested only in clinical hypertension.

JEROME M. WALDRON, M.D.

Cerebrovascular Disease. *James Peter Murphy, M.D.* Chicago, The Year Book Publishers, 1954. 408 pages, 128 figures. Price $12.00.

The field of cerebrovascular disease has been somewhat neglected during the past several decades. With the aging of our population, the number of patients who will be affected by these diseases will inevitably be markedly increased. This will result in a greater responsibility being placed upon physicians, those planning hospital facilities, economists and other groups.

This volume entitled "Cerebrovascular Diseases", by Dr. James P. Murphy is, therefore, timely. He has presented the problem systematically, beginning with the embryology and developing his subject through anatomy, physiology, etiology, pathogenesis, diagnosis, treatment and prognosis. This book is primarily a practical treatise; therefore, the author has obviously been somewhat didactic in reference to certain questions, the answers to which are not finally clarified at this time. The treatment for cerebrovascular disease is still to be regarded as being in its infancy. There is usually no definitive treatment for a hemorrhage other than that due to trauma, and in this case only if it is conveniently located for ready surgical access. The treatment for thrombosis and embolism is somewhat more amenable to approach with the advent of anticoagulants in carefully selected cases. The use of intravenous trypsin, which the author suggests, is no longer advocated by those who originally proposed it. The value of subcutaneous trypsin or other enzymes remains a matter for further investigation. The use of stellate block is still a matter of controversy and some of the surgical approaches mentioned by the author are highly experimental.

A physician reading this interesting volume must consider it in terms of an introduction to a field in which an accompanying volume could be written about what is not known. Nevertheless this useful monograph is recommended for all physicians who deal with patients suffering from cerebrovascular disease.

IRVING S. WRIGHT, M.D.

Fundamentals of Internal Medicine. *Wallace M. Yater.* Ed. 4, New York, Appleton, 1954. 1276 pages, 140 figures, and 62 tables. Price $13.50.

The fourth edition of this popular text continues the previous practice of presenting the fundamentals of internal medicine in a concise, easily readable, yet thorough fashion. Hypothetical possibilities and thoughts as to the causes and effects of disease are omitted in favor of a clear statement of what is known or known to be useful. The first 119 pages of this volume constitute the section on diseases of the heart. This chapter is largely written by Wallace M. Yater with the exception of the section on electrocardiography, which is written by Joseph M. Barker. The latest accepted methods of diagnosis and treatment are described. There has been a successful effort to present the physiologic principles upon which electrocardiography rests. There are 33 figures and one table in this chapter which well illustrate both the principles and patterns of electrocardiography.

The book in general has real advantages for both student and practitioner. The subject matter is succinctly summarized at the end of each discussion, thus giving the uninitiated student something definite to retain. Therapy in heart disease is reserved for the last 14 pages of the chapter, where it may be quickly found and quickly applied at the bedside by the busy practitioner.

In the opinion of this reviewer, this textbook offers a great deal of information, uniquely developed and presented, on the subject of heart disease.

JOSEPH A. WAGNER, M.D.

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149 GRANTS BRING 1955 RESEARCH SUPPORT TO TOTAL OF $1,419,000

One hundred and forty-nine investigators working in the cardiovascular field have been awarded grants-in-aid under the research support program of the Association and its affiliates. The grants brought to 260 the number of research awards made by the Association this year. Previously announced were 111 investigatorship and fellowship awards.

The grants have a total value of $723,972.45. In all, the National Office has awarded $1,418,-972.45 for research support, nearly 50% more than the $990,056 allotted last yea.r The overall total of research support by Heart Associations since the A.H.A. became a national voluntary health agency in 1948 is now close to the $11-million mark.

The awards made this year are supporting research during the fiscal year which began this July 1. Funds were made available from public contributions to the 1954 Heart Fund. Association policy provides for the designation of at least half of all National Office income from the Heart Fund to research support.

In general, the Association's grants provide the tools of research—equipment, laboratory supplies and technical assistance—to experienced investigators. Grants are made in varying amounts up to $10,000.

The grants were made to support investigation in virtually every known biologic and allied discipline. Many fall within the realm of basic research of a long-range character designed to broaden the scope of knowledge on the functioning of the cardiovascular system in both health and disease. Grants will aid research in the chemical, metabolic and electrical processes involved in heart action. Others are made, for projects designed to study the role of the nervous system in elevation and lowering of blood pressure; the nature of blood clotting as it relates to thrombosis; the role of endocrine action in cardiovascular diseases; and immunity factors in the causation of rheumatic fever.

The grants also provide for extensive inquiry into the causes of atherosclerosis; comparisons of varying clinical methods of rheumatic fever treatment; and techniques of cardiovascular surgery, including the employment of blood vessel grafts, hypothermia and extra-corporeal circulation.

Several of the grantees on the national list are being supported entirely or in part by local Heart Associations. They include Dr. Reno R. Porter, by the Virginia Heart Association, which is also aiding Dr. Philip Y. Paterson, an established investigator; Dr. Arthur E. McElfresh, Jr., by the Lehigh Valley (Pa.) Association; and Dr. Carl F. Schmidt, by the Burlington County (N.J.) chapter.

A complete list of grantees and the subjects of their studies is presented at the end of this section.

DEADLINE NEARS FOR APPLYING FOR 1956 FELLOWSHIP AWARDS

The application deadline for research investigatorships and fellowships to be awarded next year by the Association is September 15. Applications for grants-in-aid to be made in 1956 must be submitted by November 1, 1955. The awards will support research for the fiscal year, July 1, 1956 to June 30, 1957. They are made in the following categories:

Established Investigatorships: Awarded for periods of up to five years, subject to annual review, in amounts ranging from $6,000 to $9,000, to scientists of proven ability, who have developed in their research careers to the point where they are independent investigators.

Research Fellowships: Awarded to young men and women with doctoral degrees for periods of one to two years to enable them to train as investigators under experienced

supervision. Stipends range from $3,500 to $5,600.

Grants-in-Aid: Made to experienced investigators to provide support for specific projects, in varying amounts up to $10,000.

The Association also maintains another and unique form of research support, the Career Investigatorship. This is awarded to a limited number of investigators of unusual capacity and accomplishment to assure them of financial support throughout their productive lives. Career investigators are selected on the initiative of the Research Committee.

Additional information and application blanks may be obtained from the Medical Director, American Heart Association, 44 East 23 Street, New York 10.

NEW ORLEANS MUNICIPAL AUDITORIUM TO HOUSE SCIENTIFIC SESSIONS

Because of the large advance registration for the Association's 1955 Annual Meeting and 28th Scientific Sessions in New Orleans, the Scientific and Community Program Sessions have been moved to the city's Municipal Auditorium. Originally it had been planned to hold both the Annual Meeting and the Scientific Sessions at the Jung Hotel.

Registration

The Annual Meeting and Scientific Sessions will continue from Saturday, October 22 through Wednesday, October 26. The Scientific Sessions will occupy the first three days. Persons wishing to attend are urged to register in advance. Forms for advance registration were included in the April issue of Modern Concepts of Cardiovascular Disease, the Association's monthly bulletin for physicians. Additional registration forms are available from the American Heart Association, 44 East 23 Street, New York 10.

Lecturers Designated

Two features of the Scientific Sessions will be the annual Lewis A. Conner Memorial Lecture, to be delivered by George A. Perera, M.D., Associate Professor of Medicine at the Columbia University College of Physicians and Surgeons, New York; and the George Brown Memorial Lecture, to be presented by George Burch, M.D., Henderson Professor of Medicine at the Tulane University School of Medicine, New Orleans. Dr. Perera's subject will be Primary Hypertension. Dr. Burch will speak on Plethysmography.

Among the other features of the New Orleans gathering will be special programs on nutrition and rehabilitation presented by the Council on Community Service and Education, and a joint program of the Community Service and Rheumatic Fever and Congenital Heart Disease Councils.

Mexican Tour

An 8-day post meeting medical tour of Mexico for physicians has been arranged by the Association's Medical Division. The tour will start with a flight from New Orleans to Mexico City on Thursday, October 27. It will feature a series of scientific programs arranged by the National Institute of Cardiology in Mexico City for the mornings of October 31, November 1 and 2. An optional extension of the tour from November 2 through November 4 will provide a stay in the famed Pacific resort, Acapulco. Additional information can be obtained from the Association's Medical Division.

Meeting Schedule

The tentative schedule for the Annual Meeting and Scientific Sessions follows:

Saturday, October 22 through Monday, October 24: 28th Annual Scientific Sessions.

Sunday, October 23: First Annual Program, Council on Community Service and Education.

Sunday evening, October 23: American Heart Association Annual Dinner; Presentation of Gold Heart Awards.

Monday, October 24: Joint Program—Council on Community Service and Education and Council on Rheumatic Fever and Congenital Heart Disease.

Tuesday, October 25: Assembly Panel Meetings; Assembly Luncheon.

Wednesday, October 26: Assembly Annual Meeting; Annual Meeting of Staff Conference of Heart Associations (through Friday morning, October 28).

MINNESOTA ARTERIOSCLEROSIS SYMPOSIUM SEPTEMBER 7–9

An international Symposium on Arteriosclerosis will be held in Minneapolis, September

7–9, under the joint sponsorship of the University of Minnesota and the Minnesota Heart Association.

Ancel Keys, M.D. will serve as chairman of the symposium in which medical scientists from nine states, the District of Columbia, Canada, Germany, Italy, Sweden, the Union of South Africa and the United Kingdom will participate.

The first morning of the symposium will be devoted to presentations on the research, public health, medical education and insurance aspects of arteriosclerosis, as well as on the roles of the American Heart Association and the National Heart Institute (U. S. Public Health Service) in the fight against arteriosclerosis.

The symposium will then turn to specific studies with more than 30 specialized papers scheduled.

E. Cowles Andrus, M.D., President of the American Heart Association, and Irvine H. Page, M.D., President-elect, will be among the participants, as will be Louis N. Katz, M.D., and Paul D. White, M.D., Past Presidents, and James Watt, M.D., Director of the National Heart Institute.

ELECTROCARDIOGRAPHY COURSE FOR PHYSICIANS

A course in electrocardiographic interpretation for graduate physicians will be presented next month under the direction of Louis N. Katz, M.D., Director of the Cardiovascular Department, Medical Research Institute, Michael Reese Hospital, Chicago. It will meet daily from 9 A.M. to 5 P.M. from August 22 through September 3. Further information, including application forms and copies of the lecture schedule, can be obtained from Mrs. Ana Rose, Administrative Secretary, Cardiovascular Department, Medical Research Institute, Michael Reese Hospital, Chicago 16.

MEETINGS CALENDAR

Aug. 8–11: International Medical Assoc., Los Angeles. Dr. John T. Givens, 1108 Church Street, Norfolk 10, Va.

Aug. 28–Sept. 2: Congress of Physical Medicine and Rehabilitation, Detroit. Francis Baker, 1 Tilton Avenue, San Mateo, Calif.

Sept. 12–14: Southwestern Surgical Congress, Kansas City. Dr. C. M. O'Leary, 207 Plaza Court Bldg., Oklahoma City.

Sept. 12–15: Congress of International College of Surgeons (U. S. and Canadian Sections), Philadelphia. Dr. Karl Meyer, 1516 Lake Shore Drive, Chicago 10.

Sept. 19–22: American Hospital Association, Atlantic City, N. J. Edwin L. Crosby, 18 E. Division Street, Chicago 10.

ABROAD

July 23–29: Congress of the International Society of Surgery, Copenhagen. Dr. L. Dejardin, 141 rue Delliard, Brussels, Belgium.

July 23–30: International Anatomical Congress, Paris. Prof. Gaston Cordier, 45 rue des Saints-Péres, Paris 6.

Aug. 1–6: International Congress of Biochemistry, Brussels. Prof. C. Liebecq, 17 Place Delcour, Liége, Belgium.

Aug. 8: International Conference on Peaceful Uses of Atomic Energy (sponsored by United Nations), Geneva. Prof. Walter G. Whitman, Room 3468, United Nations, New York.

Aug. 14–20: Pan American Conference on Rheumatic Diseases, Rio de Janeiro and São Paulo, Brazil. Dr. Waldemar Bianchi, 126 Avenida Franklin D. Roosevelt, Rio de Janeiro.

Aug. 20–27: Australasian Medical Congress, Sydney, N.S.W., Australia. Federal Council of B.M.A. in Australia, 135 Macquaire Street, Sydney.

Aug. 21: World Federation for Mental Health, Istanbul, Turkey. Miss E. M. Thornton, World Federation for Mental Health, 19 Manchester Street, London W.1.

Sept. 1–4: International Medical Congress, Verona, Italy. Offices of the International Verona Fair, Piazza Bra., Verona, Italy.

Sept. 2–5: International Congress of Angiology and Histopathology, Fribourg, Switzerland. Dr. Gerson, 4 rue Pasquier, Paris 8.

Sept. 2–4: International Medical Congress, Evian, France. Dr. Laouênan, Directeur, Establissement Thermal, Evian, France.

Sept. 12–17: International Congress of Neuropathology, London. Dr. W. H. McMenemey, Department of Pathology, Maida Vale Hospital, London W. 9.

Sept. 20–24: International Congress of the European Society of Haemotology, Freiburg, Germany. Prof. Dr. Ludwig Heilmeyer, Hugstetter Strasse 55, Freiburg, Germany.

Sept. 20–26: Assembly of the World Medical Association, Vienna, Austria. Dr. Louis H. Bauer, 345 East 46 Street, N. Y. 17.

Oct. 13–15: Annual Meeting of Canadian Physiological Society, London, Ontario. Dr. J. M. R.

Beveridge, Department of Biochemistry, Queen's University, Kingston, Ontario, Canada.

GRANTS LIST

Following is a complete listing of those who have been awarded grants-in-aid by the Association for research projects during the fiscal year which began July 1, 1955, and of the subjects of their studies:

Continued Grants

Jerry K. Aikawa, University of Colorado School of Medicine, Denver. Immunophysiology.

Richard J. Bing, The Medical College of Alabama, Birmingham. Myocardial metabolism, action of digitalis on cardiac proteins.

James D. Ebert, Indiana University, Bloomington. Immunochemical and physical analysis of the time of appearance, distribution, mechanism of synthesis and interaction of the contractile proteins, actin and myosin, in the morphogenesis of the heart.

Meyer Friedman, Sanford O. Byers, Mount Zion Hospital, San Francisco. Metabolism of cholesterol.

Mario Gaudino, New York University College of Medicine, New York. Intra and extracellular distribution of electrolytes in the organism as a whole and in tissues by means of radioactive indicators.

Robert A. Good, University of Minnesota, Minneapolis. Mechanisms involved in the development of necrotizing lesions of the skin, heart, kidneys and blood vessels.

Allan V. N. Goodyer, Yale University School of Medicine, New Haven. Hemodynamic factors affecting the metabolism and renal excretion of electrolytes. The influence of electrolyte abnormalities on the circulatory response to stress.

Harold D. Green, Bowman Gray School of Medicine of Wake Forest College, Winston-Salem, N. C. Analysis of the mechanism by which epinephrine produces vasodilation including a study of the reversal induced by adrenergic blocking drugs.

Arthur C. Guyton, School of Medicine, University of Mississippi, University, Mississippi. Development of methods for continuous recording of cardiac output.

John K. Hampton, Jr., Tulane University School of Medicine, New Orleans. Cardiovascular and metabolic adjustments of the rat concerned with the development of resistance to physical trauma in the Noble-Collip Drum.

K. Albert Harden, School of Medicine, Howard University, Washington, D. C. Effect of chronic pulmonary disease and chest surgery upon pulmonary and cardiac function.

Walter Heymann, University Hospitals, Babies and Children's Division, Cleveland. Regulation of blood lipid concentration with special reference to pathogenesis of nephrotic hyperlipemia.

Edwin P. Hiatt, University of North Carolina School of Medicine, Chapel Hill. Effect of partial substitution of the nitrate ion for the chloride ion on circulation and electrolyte balance with special reference to hypertension and edema.

Steven M. Horvath, College of Medicine, State University of Iowa, Iowa City. Cardiovascular adjustments to the sudden acute occlusion of the thoracic aorta and/or one or both of the vena cava.

Walter L. Hughes, Brookhaven Laboratories, Brookhaven, L. I. Influence of the environment on the affinity of hemoglobin for oxygen.

Theodore H. Ingalls, Harvard University School of Public Health, Boston. Laboratory and epidemiologic investigation of congenital heart disease.

Roger W. Jeanloz, Massachusetts General Hospital, Boston. Biologic significance of the sulfate group in heparins.

Vincent C. Kelley, University of Utah, Salt Lake City. Adrenal hormones in the blood of patients with rheumatic fever and related conditions.

Grace P. Kerby, Duke University School of Medicine, Durham, N. C. Metabolism of acid mucopolysaccharides of ground substance.

Ancel Keys, University of Minnesota, Minneapolis. Relation between mode of life, particularly diet and physical activity, to the development of degenerative heart disease, as exemplified in different populations.

Otto Krayer, Harvard Medical School, Boston. Circulatory action of the esters of protoverine and of germine.

Alexander Leaf, Massachusetts General Hospital, Boston. The volume of distribution of a large water load; and the site of action of cortisone on water excretion.

Louis Leiter, Montefiore Hospital, New York. Use of a method of measuring lower extremity blood flow (muscle flow), for study of peripheral circulation and to measure certain aspects of muscle metabolism in normal subjects and cardiac patients.

William D. Lotspeich, University of Cincinnati College of Medicine, Cincinnati. Nature of the reabsorptive mechanism for inorganic sulfate in the normal kidney.

Oliver H. Lowry, Washington University School of Medicine, St. Louis. Isolation of specific heart constituents which bind drugs.

D. Rao Sanadi, Dept. of Physiological Chemistry, University of California Medical School, Berkeley. Mechanism of pyruvate and α-ketoglutarate oxidation in heart muscle.

John R. Smith, Washington University School of Medicine, St. Louis. Experimental collagen disease. Functional and anatomic responses of the cardiovascular system in experimental animals to repeated antigenic assaults administered by various routes.

Henry Swan, University of Colorado School of Medicine, Denver. Prevention and treatment of ventricular fibrillation during hypothermia.

John Fuller Taylor, University of Louisville School of Medicine, Louisville. Investigation of the chemical and enzymatic composition of cardiac muscle granules.

James V. Warren, Duke University School of Medicine, Durham, N. C. Response of the pulmonary vascular bed to hemodynamic alterations in the systemic circulation.

Levin Lyttleton Waters, Yale University School of Medicine, New Haven. Modification of the lesions of experimental atherosclerosis.

Stanford Wessler, Harvard Medical School at Beth Israel Hospital, Boston. Investigation of intravascular coagulation induced by stasis and the clot accelerating activity of serum (SPCA) under controlled conditions. An analysis of the factors influencing this mechanism.

Walter S. Wilde, Tulane University School of Medicine, New Orleans. Effluographic determination of ion fluxes in heart muscle in relation to systole and the ECG.

Harrison Wood, Irvington House, Irvington-on-Hudson, New York. Epidemiologic studies of methods for prevention of rheumatic fever and rheumatic heart disease.

Irving S. Wright, New York Hospital, Cornell University Medical Center, New York. Electrostatic forces in blood coagulation and the mode of action of ionic anticoagulants.

New Grants

Clarence M. Agress, Veterans Administration Center, University of California, Los Angeles. Proteolytic agents in acute myocardial infarction.

Frederick W. Barnes, Jr., The Johns Hopkins Hospital, Baltimore. Regenerative cellular response to induced depletion of cellular proteins.

Samuel Bellett, Philadelphia General Hospital, Philadelphia. Therapeutic index of digitalis leaf, gitalin, digoxin, acetyl digitoxin and other digitalis preparations. An experimental and clinical study.

Earl Benditt, LaRabida Jackson Park Sanitarium, Chicago. Role of the mast cell in the acute vascular reaction to injury.

Maurice M. Best, University of Louisville School of Medicine, Louisville. Serum lipid fractions in induced and spontaneous hypothyroidism and their modifications by beta-sitosterol.

William S. Blakemore, School of Medicine, University of Pennsylvania, Philadelphia. Evaluation of freeze-dried homografts and synthetic cloth mesh materials used to replace human blood vessels.

Edward H. Bloch, Western Reserve University School of Medicine, Cleveland. In vivo control of erythrocyte aggregation. I. The influence of surface active agents on erythrocyte aggregation and the mechanism of the reaction of particulate matter with the blood and liver analyzed in vivo at the microscopic level.

J. M. B. Bloodworth, Jr., Ohio State University College of Medicine, Columbus. Chemistry, histochemistry and renal histopathology of degenerative vascular disease associated with diabetes mellitus. A human and experimental study of the Kimmersteil-Wilson syndrome.

Walter M. Booker, Howard University Medical School, Washington. Electrolyte changes in blood during hypothermia.

Gerhard A. Brecher, Western Reserve University School of Medicine, Cleveland. Dynamic aspects of blood flow in physiological and pathological states.

Robert J. Boucek, University of Miami School of Medicine, Coral Gables, Fla. Factors influencing the number of mast cells, the heparin concentration and the lipids of connective tissue of animal and man (a study in atherosclerosis).

Joel G. Brunson, University of Minnesota Medical School, Minneapolis. Experimental myocarditis and valvulitis.

Henry Mead Cavert, University of Minnesota Medical School, Minneapolis. Metabolism of cardiac tissue investigated with isotopic technics; intermediate of propionate, lactate and pyruvate metabolism in cardiac tissue.

Leon Churney, Louisiana State University School of Medicine, New Orleans. Electrical properties of normal and vagally inhibited auricular muscle.

Leland C. Clark, Jr., Fels Research Institute, Antioch College, Yellow Springs, Ohio. Bubble oxygenator and total perfusion.

David G. Cogan, Harvard Medical School, Boston. Aging processes as reflected in the cornea, specifically the relation of fat deposition in the cornea to atheroma in the blood vessels.

Sidney Cohen, Harvard Medical School, Boston. An approach to chemotherapy of infections of penicillin resistant staphylococci through the use of penicillinase inhibitors.

Dean A. Collins, Temple University School of Medicine, Philadelphia. Continuation of research on preparation and study of angiotonase (hypertensinase).

Hadley L. Conn, Jr., University of Pennsylvania School of Medicine, Philadelphia. Utilization of radio-isotope technics in the study of shock incident to acute cardiovascular stress.

T. S. Danowski, University of Pittsburgh School of Medicine, Pittsburgh. Hemodialysis in chronic, far-advanced but not terminal renal failure.

Ralph A. Deterling, Jr., Columbia University College of Physicians and Surgeons, New York. Continuation of development of plastic prostheses for blood vessel replacement and aortic insufficiency; investigation of possible application of controlled cross-circulation to surgery of acquired heart disease.

Carl Djerassi, Wayne University, Detroit. Chemical studies on hypotensive alkaloids.

F. Curtis Dohan, University of Pennsylvania, Philadelphia. Urinary excretion of specific alpha-ketolic

steroids in 'normal' individuals of various age groups.

Anastasius S. Dontas, University of Michigan, Ann Arbor. Electrophysiologic study of antihypertensive agents; dynamics of prolonged altered cardiovascular homeostasis.

Douglas R. Drury, Kerckhoff Laboratories, Los Angeles. Investigation of genetic and environmental factors in the production of hypertension; cardiovascular responses and effects of lowering blood pressure in a colony of spontaneously hypertensive rabbits.

Isidore S. Edelman, San Francisco City and County Hospital, San Francisco. Fluid and electrolyte anatomy in patients with essential hypertension.

H. E. Ederstrom, University of North Dakota School of Medicine, Grand Forks. In vitro changes in blood vessels from normal chronically denervated or sympathectomized parts of dogs, cats and man.

J. Russell Elkinton, Hospital of the University of Pennsylvania, Philadelphia. Supra-optico-hypophyseal system in the normal dog, cat and rat pertaining to volume and concentration regulation; an effort to provide at least a partial explanation of certain phenomena observed in markedly edematous patients with heart disease.

Robert S. Ely, University of Utah, Salt Lake City. Evaluation of corticosterone metabolism in patients with rheumatic fever.

Sasha Englard, Albert Einstein School of Medicine, New York. Mechanism of hydrogen transport as mediated by flavin containing systems, and mechanism of action of aconitase and isocitric dehydrogenase, from heart muscle.

Alfred Farah, State University of New York, Syracuse. Factors influencing the treppe and after-stimulation contraction in cardiac muscle.

George Fawaz, American University of Beirut, Beirut, Lebanon. Effect of Kreb cycle inhibitors and metabolites on the performance and metabolism of the isolated mammalian heart (heart-lung preparation).

Henry Field, Jr., Veterans Administration Hospital, Martinsburg, West Virginia. Electrolyte studies, including biochemical, physicochemical and hormonal influences, operative in congestive heart failure and in other conditions of electrolyte imbalance.

Alfred P. Fishman, Columbia University College of Physicians and Surgeons and Presbyterian Hospital, New York. Relationships between ventilation and pulmonary blood flow in normal man and in patients with chronic cardio-pulmonary disease.

W. Horsley Gantt, Johns Hopkins University School of Medicine, Baltimore. Modification of tachycardia and hypertension psychogenically produced.

Joseph J. Garamella, Mount Sinai Hospital, Minneapolis. Development of a method for controlled chronic progressive coronary artery occlusion.

Robert P. Glover, The Presbyterian Hospital, Philadelphia. Experimental study of aortic valvular disease.

David A. Goldthwait, Western Reserve University, Cleveland. Biosynthesis of purine nucleotides.

Frank D. Gray, Jr., Yale University School of Medicine, New Haven. Electrolyte and acid-base balance in chronic cor pulmonale.

John W. Hall, New York University College of Medicine, New York. Experimental study of pulmonary hemodynamics by measurement of pulmonary compliance.

Calvin Hanna, University of Tennessee, Memphis. Studies on tachyphylaxis.

Mary Ellen Hartman, Temple University School of Medicine, Philadelphia. Quantitation of the capillary responses in the mammalian glomerulus under normal and experimental conditions.

Stewart C. Harvey, University of Utah, College of Medicine, Salt Lake City. A. Pharmacology, physiology and biochemistry of the heart (II. Research on the mechanism of action of digitalis.) B. Studies on autonomic cardiovascular agents.

John B. Hickam, Duke University School of Medicine, Durham, N. C. Pulmonary hemodynamics by measurement of pulmonary compliance.

Joseph P. Holt, University of Louisville Institute for Medical Research, Louisville. Studies on the venous system in dogs and man with special reference to the collapsibility of veins, and how this effects the pressure and flow through the venous system.

C. Riley Houck, University of Tennessee, Memphis. Origin of hypertension in the chronic bilaterally nephrectomized dog.

O. Henry Janton, The Presbyterian Hospital, Philadelphia. Clinical and detailed objective study of patients having undergone mitral commissurotomy five years ago.

Richard J. Jones, University of Chicago, Chicago. Identification of the hypocholesteremic agent in a brain extract and studies on its mode of action.

Alex Kaplan, Medical Research Institute, Michael Reese Hospital, Chicago. Role of adrenal medullary and cortical hormones in the regulation of lipid metabolism.

Melvin H. Kaplan, House of the Good Samaritan, Boston. Localization of streptococcal antigens and antibodies in tissues by means of the fluorescein-labeling technique.

Louis N. Katz, Cardiovascular Department, Michael Reese Hospital, Chicago. Coronary circulation, cardiac energetics and myocardial metabolism.

John H. Keating, St. Luke's Hospital, New York. Renal hemodynamics, acid-base balance and electrolyte excretion.

F. E. Kelsey, University of South Dakota Medical School, Vermillion. Mechanism of action of digitoxin and related substances.

Walter M. Kirkendall, State University of Iowa General Hospital, Iowa City. Effects of drug and

surgical therapy on renal circulation and function in certain cardiovascular disorders.

Peter K. Knoefel, University of Louisville School of Medicine, Louisville. Extent and nature of the involvement of the kidney in certain changes in the dog's circulation.

Harvey C. Knowles, Jr., University of Cincinnati College of Medicine, Cincinnati, to study the occurrence and distribution of carotenoid pigments in atherosclerosis in humans.

Charles D. Kochakian, Oklahoma Medical Research Foundation, Oklahoma City. Role of steroid hormones in the regulation of the biochemistry of the heart.

Charles E. Kossman, New York University College of Medicine, New York. Correlation of intracellular potential variations of the single ventricular fiber with mechanical function of the ventricles.

William J. Kuhns, University of Pittsburgh Medical Center, Pittsburgh. Immunochemical studies of human diphtheria antitoxins—investigation of toxin-antitoxin complexes.

Peter T. Kuo, Hospital and School of Medicine, University of Pennsylvania, Philadelphia. Investigation of vascular fluid dynamics, their influences upon the intravascular distribution of plasma lipids, and their relationship to the problem of atherosclerosis.

Willoughby Lathem, Yale University School of Medicine, New Haven. Measurement of splanchnic red blood cell and plasma volumes and of the splanchnic hematocrit in congestive heart failure.

Abel Alfred Lazzarini, Jr., Bellevue Medical Center, Post Graduate Medical School, New York. Metabolic and immunological changes occurring in transplanted tissues.

Richard E. Lee, Cornell University Medical College, New York. Nature, source, and role of the plasma epinephrine-like factor in experimental and clinical hypertensive disease.

Eugene Lepeschkin, University of Vermont College of Medicine, Burlington. Differentiation between organic and functional systolic murmurs by means of esophageal calibrated phonocardiography, correlated with blood viscosity.

Arthur E. McElfresh, Jr., St. Christopher's Hospital for Children, Philadelphia. Nature and significance of the hemolytic factor in acute rheumatic fever.

Johnson McGuire, University of Cincinnati, Cincinnati General Hospital, Cincinnati. Pulmonary function in heart disease.

John P. Merrill, Peter Bent Brigham Hospital, Boston. Investigation of the relation of renal failure to certain disorders of the cardiovascular system.

William F. Miller, University of Texas, Southwestern Medical School, Dallas. I. The development of an improved method of measuring arterial oxygen tension at all levels of oxygenation. II. The role of oxygen in the treatment of acute pulmonary edema.

William R. Milnor, Johns Hopkins University School of Medicine, Baltimore. Regional blood volumes in congenital and acquired heart disease.

Wilfried F. H. M. Mommaerts, Western Reserve University School of Medicine, Cleveland. Chemical-physiologic and biophysic studies related to the problem of contractility.

Ian Whitelaw Monie, University of California, Berkeley. Detailed study of the cardiovascular anomalies of rat embryos from mothers deprived of pteroylglutamic acid (PGA) during part of pregnancy.

Hugh Montgomery, Hospital of the University of Pennsylvania, Philadelphia. Influence of Buerger's exercises and of the oscillating bed on blood flow and oxygen tension of the skin of the digits of ischemic extremities.

R. David Nelson, Bethel College, Saint Paul, Minnesota. Further investigation into the chemistry of phenothiazine and its derivatives, as well as a study of structurally related compounds.

Robert E. Olson, University of Pittsburgh, Pittsburgh. Effect of congestive heart failure due to valvular disease upon myocardial metabolism in dogs.

Akira Omachi, Stritch School of Medicine of Loyola University, Chicago. Electrolyte metabolism in the isolated mammalian heart.

John J. Osborn, Stanford University Hospitals, San Francisco. Repair of congenital cardiac defects under direct vision with extracorporeal circulation and oxygenation with and without hypothermia.

Abraham G. Osler, Johns Hopkins University School of Hygiene and Public Health, Baltimore. Mechanism of hypersensitivity reactions.

Richard R. Overman, University of Tennessee, College of Medicine, Memphis. Mechanisms of ionic distribution in experimental cardiovascular disorders.

Sam Paplanus, Vanderbilt University School of Medicine, Nashville, Tenn. Effect of chronic anemia on the size of the heart.

Reno R. Porter, Medical College of Virginia, Richmond. Effects of alterations in adrenal blood flow on renal function.

Isadore N. Rosenberg, Boston City Hospital, Boston. Endocrine factors in lipid metabolism.

Ray H. Rosenman, Harold Brunn Institute, Mount Zion Hospital, San Francisco. Mechanism of hypercholesteremia and hyperlipemia in experimental nephrosis in rats.

Abraham M. Rudolph, Harvard Medical School, Children's Medical Center, Boston. Pulmonary hypertension in congenital heart disease.

Robert F. Rushmer, University of Washington, Seattle. Factors influencing diastolic filling and systolic emptying of the ventricular chambers.

David D. Rutstein, Harvard University Medical School, Boston. Effects of rheumatic fever serum and steroid compounds on human heart muscle in tissue culture.

David D. Rutstein, Cooperative Rheumatic Fever Study, New York. Relative effectiveness of ACTH,

cortisone and aspirin therapy of rheumatic fever in the prevention of rheumatic heart disease.

Leo A. Sapirstein, Ohio State University, Columbus. Mechanisms of sodium elimination.

Allen M. Scher, University of Washington School of Medicine, Seattle. Body surface potentials produced by an intracardiac dipole.

Carl F. Schmidt, University of Pennsylvania School of Medicine, Philadelphia. Physiology and pharmacology of the coronary circulation, with special reference to the influence of mechanical and nervous factors.

Bodil Schmidt-Nielsen, Duke University, Durham, N. C. Comparative studies on the renal function in various animals with special emphasis on the mechanism for urea excretion as related to protein metabolism.

William B. Schwartz, New England Center Hospital, Boston. Acid-base regulation by the kidney and tissues.

B. H. Scribner, University of Washington School of Medicine, Seattle. Practical problems in the management of fluid electrolyte therapy.

Alvin P. Shapiro, Southwestern Medical School of the University of Texas, Dallas. Controlled study in the rat of the relationship between hypertensive vascular disease and experimental chronic pyelonephritis.

Robert S. Shaw, Massachusetts General Hospital, Boston. Grafting of valve-containing veins into veins.

Thomas P. Singer, Edsel B. Ford Institute for Medical Research, Henry Ford Hospital, Detroit. A. The succinic oxidase of the heart muscle. B. Mechanism of SO_2 fixation in animal tissue.

Jay A. Smith, Chicago Medical School, Chicago. Effect of various substances on the increase in metabolic rate due to ouabain as measured in the cartesian diver.

Nathan J. Smith, University of California at Los Angeles. Investigation into certain hematological aspects of cyanotic types of heart disease.

Richard T. Smith, University of Minnesota, Minneapolis. Origin and significance of a heparin precipitable form of fibrinogen occurring in human rheumatic fever and other diseases, and experimentally in endotoxin treated rabbits.

Merrill P. Spencer, Bowman Gray School of Medicine, Wake Forest College, Winston-Salem, N. C. Direct measurement of blood flow in humans.

Jeremiah Stamler, Cardiovascular Department, Michael Reese Hospital, Chicago. Pathophysiologic homeostasis of renal function and water-electrolyte metabolism in experimental congestive circulatory failure with edema.

Paul Starr, Los Angeles County General Hospital, Los Angeles. Effect of thyroid hormone on the cardiovascular system: triiodothyronine.

Mario Stefanini, Saint Elizabeth Hospital, Boston. For the identification and purification of substances causing the activation of fibrinolysin in man and their use in the control and treatment of thromboembolic conditions.

Albert Szent-Györgyi, Institute for Muscle Research, Woods Hole, Mass. Chemical, macromolecular and histological structure of muscle and chemistry of contraction cycle: mechano-chemical coupling.

Andrew Szent-Györgyi, Institute for Muscle Research, Woods Hole, Mass. Structure and function of the contractile proteins of muscle.

C. Bruce Taylor, The Presbyterian Hospital of the City of Chicago. Atherosclerosis and lipid metabolism in the macacus rhesus monkey.

Lewis Thomas, New York University College of Medicine, New York. Mechanisms of tissue damage in bacterial infection and hypersensitivity.

Louis Tobian, University of Minnesota School of Medicine, Minneapolis. Physiology of the renal anti-hypersensitive mechanism in man and experimental animals.

Kurt N. Von Kaulla, University of Colorado School of Medicine, Denver. Fibrinolytic enzymes.

Richard W. Von Korff, University of Minnesota, Minneapolis. Studies on intermediary metabolism.

G. E. Wakerlin, University of Illinois College of Medicine, Chicago. Pathogenesis and treatment of experimental hypertension produced by constriction of the carotid sinus area.

William B. Wartman, Northwestern University Medical School, Chicago. Cytochemical changes that take place in the myocardium during injury, with special reference to ischemia and hypertrophy.

Charles M. Wilhelmj, Creighton University School of Medicine, Omaha, Neb. Role of diet, emotional tension and the autonomic nervous system as etiologic factors in hypertension.

Harold A. Zintel, St. Luke's Hospital, New York. Investigation of synthetic prosthetic tubes for the repair of arterial defects.

Marjorie B. Zucker, New York University College of Dentistry, New York. Mechanism of hemostasis, with particular reference to the effect of dextran and crystalline fibrinolysin.

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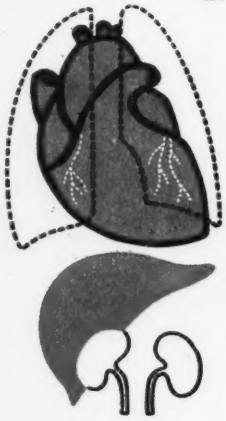

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